

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
2 December 2010 (02.12.2010)

PCT

(10) International Publication Number  
**WO 2010/138600 A2**

(51) International Patent Classification:

A61K 45/06 (2006.01) A61K 31/4245 (2006.01)  
A61P 29/00 (2006.01) A61K 31/4427 (2006.01)  
A61P 25/04 (2006.01)

(21) International Application Number:

PCT/US2010/036213

(22) International Filing Date:

26 May 2010 (26.05.2010)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/182,264 29 May 2009 (29.05.2009) US

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(81) Designated States (unless otherwise indicated, for every

kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every

kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to the identity of the inventor (Rule 4.17(i))
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

- without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF PAIN

(57) Abstract: This invention discloses a method of treatment of osteoarthritis pain by administration of a composition containing a nicotinic acetylcholine receptor ligand and a nicotinic acetylcholine receptor subtype 4 2 allosteric modulator. The present application also relates to compositions comprising such compounds for use in treating pain and related disorders mediated by controlling neurotransmitter release in a subject.



WO 2010/138600 A2

## PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF PAIN

### Cross-Reference to Related Applications

This patent application claims priority to U.S. Provisional Patent Application No. 61/182,264, filed on May 29, 2009, the entirety of which is incorporated herein by reference.

5

### BACKGROUND OF THE INVENTION

#### Technical Field

10 The invention relates to methods of treating pain. More particularly, the invention relates to compositions comprising an  $\alpha 4\beta 2$  positive allosteric modulator in combination with an  $\alpha 4\beta 2$  receptor ligand, methods of preparation of such compositions, and their use in the treatment of pain.

#### Description of Related Technology

15 Pain is the most common symptom of disease and the most frequent complaint with which patients present to physicians. Pain is commonly segmented by duration (acute vs. chronic), intensity (mild, moderate, and severe), and type (nociceptive vs. neuropathic).

20 Nociceptive pain is the most well known type of pain, and is caused by tissue injury detected by nociceptors at the site of injury. After the injury, the site becomes a source of ongoing pain and tenderness. Nociceptive pain can be experienced as sharp, dull, or aching. This pain and tenderness are considered "acute" nociceptive pain. This pain and tenderness gradually diminish as healing progresses and disappear when healing is complete. Examples of acute nociceptive pain include surgical procedures (post-op pain), burns, ocular pain, inflammation (due to infection or arthritis) and bone fractures. Even though there may be no  
25 permanent nerve damage, "chronic" nociceptive pain results from some conditions when pain extends beyond six months. Examples of chronic nociceptive pain include osteoarthritis, rheumatoid arthritis, and musculoskeletal conditions (e.g., back pain), cancer pain, etc.

Neuropathic pain is defined as “pain initiated or caused by a primary lesion or dysfunction in the nervous system” by the International Association for the Study of Pain. Neuropathic pain may refer to peripheral neuropathic pain, which is caused by damage to nerves, or to central neuropathic pain, which is caused by damage to the brain, brainstem, or spinal cord. Neuropathic pain is not associated with nociceptive stimulation, although the passage of nerve impulses that is ultimately perceived as pain by the brain is the same in both nociceptive and neuropathic pain. The term neuropathic pain encompasses a wide range of pain syndromes of diverse etiologies. The three most commonly diagnosed pain types of neuropathic nature are diabetic neuropathy, cancer neuropathy, and HIV pain. In addition, neuropathic pain is diagnosed in patients with a wide range of other disorders, including fibromyalgia, trigeminal neuralgia, post-herpetic neuralgia, traumatic neuralgia, phantom limb, headaches, as well as a number of other disorders of ill-defined or unknown origin.

Neuronal nicotinic receptors, especially  $\alpha 4\beta 2$  neuronal nicotinic acetylcholine receptors (nAChRs) have been targeted for pain and various other central nervous system diseases. Antisense knockdown of the  $\alpha 4$  subunit was found to decrease the analgesic effect of agonists (Bitner RS, et al., *Brain Res.* 871:66-74, 2000). Reduced antinociceptive responses to nicotine also is seen in  $\alpha 4$  gene knockout animals (Marubio LM, et al., *Nature* 398:805-810, 1999). Both  $\alpha 4$  and  $\beta 2$  nAChRs are responsible for mediating nicotinic analgesia at supraspinal responses and spinal sites (Decker, MW, et al., *Curr Top Med Chem.*, 4: 369-384, 2004). Antinociceptive effects through  $\alpha 4\beta 2$  nAChRs are generally attributed to stimulation of brainstem monoaminergic transmission, particularly in the raphe (Cucchiario G, et al., *J Pharmacol Exp Ther.* 313:389-394, 2005). However,  $\alpha 4\beta 2$  stimulation of GABAergic and glycinergic inhibitory transmission in the spinal cord also may contribute (Rashid MH, et al., *Pain* 125:125-135, 2006).

Central  $\alpha 3^*$  nAChRs may contribute to nicotinic analgesia (Khan IM, et al., *J Neurocytol.* 33:543-556, 2004), but  $\alpha 3\beta 4$  ligands are of little interest because of likely autonomic side effects. Indeed, the goal has been to avoid  $\alpha 3^*$  neuronal nicotinic receptor (NNR), as the dose-limiting emetic liability of nonselective compounds has been attributed to activation of  $\alpha 3$  containing nAChRs.  $\alpha 3^*$  nAChRs are expressed in the enteric nervous system as well as in other components of the peripheral and central nervous systems. Area postrema and nucleus tractus solitarius are brainstem nuclei thought to be involved in nausea and emesis.  $\alpha 3^*$  nAChRs in the dorsal motor nucleus of the vagus and in nucleus tractus

solitarius have been implicated in gastric and blood pressure responses to nicotine injected locally (Ferreira M, et al *J. Pharmacol. Exp. Ther.*, 294:230-238, 2000).

Compounds with varying degrees of selectivity for  $\alpha 4\beta 2$  nAChRs over other nicotinic subtypes ( $\alpha 3$ ,  $\alpha 7$ ,  $\alpha 1$ -containing) have been discovered over the years. For example, ABT-594 (referred to as Compound A in this application) was efficacious across a number of rodent models of nociception including acute thermal, chemogenic, neuropathic, and visceral pain (Decker MW, et al., *Expert Opinion on Investigational Drugs*, 10:1819-1830, 2001). Available data suggest that ligands with selectivity for the  $\alpha 4\beta 2$  nAChRs over  $\alpha 3\beta 4$  efficacy is preferred for low adverse event profiles. In theory, the therapeutic index could be expanded by (a) reducing  $\alpha 3\beta 4$  activity or (b) increasing  $\alpha 4\beta 2$  efficacy without increasing  $\alpha 3\beta 4$  activity. The latter may be achieved by an  $\alpha 4\beta 2$  selective positive allosteric modulator (PAM) either alone or in combination with exogenous  $\alpha 4\beta 2$  agonist. Positive allosteric modulators can potentiate effects by enhancing the efficacy and or potency of agonists. Accordingly, an  $\alpha 4\beta 2$  selective positive allosteric modulator can selectively enhance effects at the preferred  $\alpha 4\beta 2$  nAChRs over other nAChR subtypes.

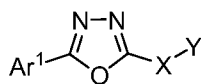
Initially known positive allosteric modulators of the  $\alpha 4\beta 2$  nAChRs have been nonselective and not very potent. For example, nefiracetam has been reported to potentiate  $\alpha 4\beta 2$  nAChR responses (Narahashi T, et al., *Biol.Pharm.Bull.*, 27:1701-1706, 2004). More recently, subtype selective PAMs have been disclosed. Compounds like 3-(3-pyridin-3-yl-1,2,4-oxadiazol-5-yl) benzonitrile and others have been described with robust  $\alpha 4\beta 2$  PAM effects with little modulatory activity at other subtypes such as  $\alpha 3\beta 4$  (e.g., see WO 2006/114400, published November 2, 2006, incorporated herein by reference in its entirety).

Pain is an unmet medical need and the methods and possibilities for treatments of such indications are insufficient. Although continued efforts are being made to treat pain using nAChR agonists, robust efficacy in pain may be limited by the range of side effects associated with their use, albeit to differing degrees. In light of the significance of chronic pain and the limitations in their treatment, it would be beneficial to identify new methods of treating such disorders, particularly in a manner that reduces adverse ganglionic effects such as at the gastrointestinal systems (e.g. emesis). It would be particularly beneficial to identify compounds and compositions that offer an opportunity to widen the therapeutic window of nicotinic (nAChR) agonists in pain. Enhanced efficacy with nAChR ligands for the treatment of other central nervous system diseases such as cognitive and attention deficits is also desirable.

SUMMARY OF THE INVENTION

This invention provides methods and compositions for inducing, promoting or otherwise facilitating pain relief. In one embodiment, the present invention relates to methods for treating or preventing pain, including nociceptive and/or neuropathic pain in mammals, and particularly in humans, comprising: (i) administering a nicotinic acetylcholine receptor ligand; and (ii) administering a nicotinic acetylcholine receptor subtype  $\alpha 4\beta 2$  allosteric modulator to the mammal in an amount effective to treat the pain. More particularly, the present method relates to the treatment of osteoarthritis pain by administering a therapeutically effective amount of a nicotinic acetylcholine receptor subtype  $\alpha 4\beta 2$  allosteric modulator, or a salt thereof, in combination with a nicotinic acetylcholine receptor ligand, or a salt thereof, to a subject in need of treatment.

Suitable nicotinic acetylcholine receptor subtype  $\alpha 4\beta 2$  selective positive allosteric modulators are, for example, compounds of formula (I):



(I)

or are pharmaceutically acceptable salts and prodrugs thereof, wherein

X is a bond, O,  $\text{NR}^1$ , S, or  $\text{C}_1\text{-C}_3$  alkylene;

Y represents a monocyclic aryl, cycloalkyl, heterocycle, or heteroaryl group;

$\text{Ar}^1$  represents a monocyclic aryl or a heteroaryl group; and

$\text{R}^1$  is hydrogen, alkyl, haloalkyl or arylalkyl.

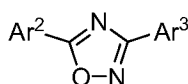
X is selected from a bond, O,  $\text{NR}^1$ , S, or  $\text{C}_1\text{-C}_3$  alkylene, wherein  $\text{R}^1$  is selected from hydrogen, alkyl, haloalkyl, and arylalkyl. Preferably, X is a bond. Preferably,  $\text{R}^1$  is hydrogen or alkyl.

Y represents a monocyclic aryl, cycloalkyl, heterocycle, or heteroaryl group, which can be substituted or unsubstituted with substituents. Examples of suitable heterocycle groups can include, but are not limited to, pyrrolidine, piperidine, and the like. Examples of suitable heteroaryl groups can include, but are not limited to, thienyl, furanyl, pyridinyl, pyrazinyl, and the like. A preferred monocyclic aryl group is substituted or unsubstituted phenyl. Suitable substituents for the monocyclic aryl, heterocycle, or heteroaryl group are,

for example, alkyl, cycloalkyl, cycloalkylalkyl, halo, haloalkyl, hydroxyl, alkoxy, haloalkoxy, nitro, and cyano.

Ar<sub>1</sub> represents a monocyclic aryl, such as substituted or unsubstituted phenyl, or heteroaryl group. Examples of suitable heteroaryl groups include, but are not limited, thienyl, furanyl, pyrrolyl, pyrazolyl, thiazolyl, 1,3,4-thiadiazolyl, and pyridinyl, each of which can be unsubstituted or substituted with one, two, or three substituents selected from alkyl, cycloalkyl, cycloalkylalkyl, halo, haloalkyl, hydroxyl, alkoxy, haloalkoxy, nitro, cyano, and amino.

Yet other suitable examples of  $\alpha 4\beta 2$  positive allosteric modulators include, but are not limited to, compounds of the formula (II):



(II)

or are pharmaceutically acceptable salts thereof, wherein

Ar<sup>2</sup> is aryl or heteroaryl, wherein the aryl or heteroaryl is substituted or unsubstituted, and, when substituted, the aryl or heteroaryl is substituted with 0, 1, 2, 3, or 4 substituents selected from halo, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>6</sub>-C<sub>10</sub> aryl, C<sub>4</sub>-C<sub>7</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>5</sub>-C<sub>10</sub> heteroaryl, C<sub>4</sub>-C<sub>10</sub> heterocycle, C<sub>1</sub>-C<sub>6</sub> alkyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl)NHC(O)O-(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl, amino, hydroxyl, haloalkyl-C(O)-, haloalkyl-SO<sub>2</sub>-, alkyl-SO<sub>2</sub>-, -SO<sub>2</sub>NH<sub>2</sub>, -SO<sub>2</sub>NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -SO<sub>2</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, cyano, nitro, C<sub>1</sub>-C<sub>6</sub> acylamino, C<sub>1</sub>-C<sub>6</sub> alkoxy, -C(O)NH<sub>2</sub>, -C(O)O-(C<sub>1</sub>-C<sub>6</sub> alkyl), and carboxy; and

Ar<sup>3</sup> is aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted, and, when substituted, the aryl or heteroaryl is substituted with a substituent selected from halo, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>6</sub>-C<sub>10</sub> aryl, C<sub>4</sub>-C<sub>7</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>5</sub>-C<sub>10</sub> heteroaryl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, amino, hydroxyl, haloalkyl-SO<sub>2</sub>-, cyano, nitro, C<sub>1</sub>-C<sub>6</sub> acylamino, C<sub>1</sub>-C<sub>6</sub> alkoxy, -N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, and carboxy.

Preferably, the nicotinic acetylcholine receptor ligand is a neuronal nicotinic receptor subtype  $\alpha 4\beta 2$  ligand. Accordingly,  $\alpha 4\beta 2$  receptor ligands suitable for the invention can be compounds of various structural classes. Particularly, some examples of  $\alpha 4\beta 2$  receptor ligands suitable for the invention include, but are not limited to heterocyclic ether derivatives (see, for example, International Publication No. WO 99/32480, published July 1, 1999; U.S. Patent No. 5,948,793, issued September 7, 1999, and U.S. Patent No 5,914,328, issued June 22, 1999); N-substituted diazabicyclic derivatives (see, for example, International Publication

No. WO 2004/0186107, published September 23, 2004, and U.S. Patent No. 6,809,105, issued October 26, 2004); heterocyclic substituted amino azacycles (see, for example, International Publication No. WO 00/71534, published November 30, 2000, and U.S. Patent No. 6,833,370, issued December 21, 2004); all of which are hereby incorporated by reference  
5 in their entirety. Further description and methods for preparing the compounds have been reported in the patents, patent publications, and international patent publications cited.

Additional examples of  $\alpha 4\beta 2$  receptor ligands suitable for the invention include, but are not limited to aryl-fused azapolycyclic compounds (see for example, International Publication No. WO 2001062736, published August 30, 2001); aryl-substituted olefinic  
10 amine compounds (see for example, International Publication Nos. WO 9965876, published December 23, 1999, and WO 00/75110, published December 14, 2000); pyridopyranoazepine derivatives (see for example, US Patent No. 6,538,003, published March 25, 2003); benzylidene- and cinnamylidene- anabaseines (see for examples, International Publication No. WO 99/10338, published March 4, 1999); and 3-pyridoxylalkyl heterocyclic ether  
15 compounds (see for example, International Publication No. WO 96/040682, published December 19, 1996); all of which are hereby incorporated by reference in their entirety. Further description and methods for preparing the compounds have been reported in the patents and international patent publications cited.

In other embodiments, the invention relates to compositions for treating or preventing  
20 pain, particularly osteoarthritis pain, comprising (i) a nicotinic acetylcholine receptor ligand; and (ii) a nicotinic acetylcholine receptor subtype  $\alpha 4\beta 2$  selective positive allosteric modulator. The compositions of the present invention are useful in the treatment pain or disease states related to the nicotinic acetylcholine receptor (nAChR) with enhanced efficacy and reduced side effects than nicotinic agents alone. The invention is most beneficial  
25 wherein the amounts of (i) and (ii) together are effective in treating nAChR-mediated disease states.

As such, the invention relates to a composition for treating or preventing pain wherein the efficacy of a nicotinic (nAChR) agent is enhanced by co-dosing a nicotinic ligand with a positive allosteric modulator (PAM) of nAChR subtype  $\alpha 4\beta 2$ . The invention relates to  
30 compositions for treatment of individuals with nAChR-mediated diseases or disorders, and particularly for pain, which involves a combination of a nicotinic ligand with an  $\alpha 4\beta 2$  positive allosteric modulator. The invention provides a synergistic combination of an  $\alpha 4\beta 2$  nicotinic agonist or partial agonist with an  $\alpha 4\beta 2$  positive allosteric modulator. Such

combination enhances the efficacy of  $\alpha 4\beta 2$ s ligand and can provide a beneficial alternative to current treatments.

Yet another embodiment of the invention relates to an article of manufacture for the treatment of pain, comprising: (i) a first pharmaceutical dosage form comprising at least one  
5 nicotinic acetylcholine receptor ligand; (ii) a second pharmaceutical dosage form comprising at least one nicotinic acetylcholine receptor subtype  $\alpha 4\beta 2$  positive allosteric modulator, wherein the article contains first and second pharmaceutical dosage forms.

The embodiments of the invention, how to prepare them, and how to use them are further described herein.

10

#### BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B depict responses of a representative nicotinic acetylcholine receptor ligand, 5-[(2R)-azetidin-2-ylmethoxy]-2-chloropyridine (Compound A) in the  
15 absence and presence of a nicotinic acetylcholine receptor subtype  $\alpha 4\beta 2$  positive allosteric modulator, 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile (PAM, Compound 1), at human  $\alpha 4\beta 2$  or  $\alpha 3\beta 4$  nicotinic acetylcholine receptor subtypes expressed in HEK-293 cells. The data demonstrate a leftward shift in potency ( $EC_{50}$  value) at  $\alpha 4\beta 2$ , but not  $\alpha 3\beta 4$ , nAChRs.

20

Figures 2A and 2B depict responses of another representative nicotinic acetylcholine receptor ligand, (3R)-1-pyridin-3-ylpyrrolidin-3-amine (Compound B), in the absence and presence of an  $\alpha 4\beta 2$  positive allosteric modulator, 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile (PAM, Compound 1), at human  $\alpha 4\beta 2$  or  $\alpha 3\beta 4$  nicotinic receptor subtypes expressed in HEK-293 cells. Again, the data demonstrate a leftward shift in potency ( $EC_{50}$   
25 value) of the nAChR agonist at  $\alpha 4\beta 2$ , but not  $\alpha 3\beta 4$  nAChRs.

25

Figures 3A and 3B graphically represent the effect of  $\alpha 4\beta 2$  positive allosteric modulator in enhancing the effect of a nAChR partial agonist, such as 2-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine (Compound C, also known as ABT-089; Reuter, L.E., et al., *CNS Drug Rev.*, 10 (2), 167-182, 2004). Compound C alone does not evoke a calcium  
30 response, but when co-applied with the PAM, 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile (Compound 1), evoked robust responses at  $\alpha 4\beta 2$  nAChRs (Figure 3A), but not at  $\alpha 3\beta 4$  nAChRs (Figure 3B). Compound C is a representative of other nicotinic partial agonists.

30

Figures 4A and 4B graphically represent the effect of an  $\alpha 4\beta 2$  positive allosteric modulator in enhancing the effect of another nAChR partial agonist (1S,5S)-3-(3,6-diazabicyclo[3.2.0]hept-3-yl)-quinoline (Compound D;  $\alpha 4\beta 2$  [ $^3\text{H}$ ]cytisine  $K_i = 6$  nM)). Compound D alone does not evoke a response, but when co-applied with the PAM, 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile (Compound 1), evoked robust responses at  $\alpha 4\beta 2$  nAChRs (Figure 4A), but not at  $\alpha 3\beta 4$  nAChRs (Figure 4B). Compound D is a representative of other nicotinic partial agonists.

Figure 5 shows correlation of potencies for activation of  $\alpha 4\beta 2$  nAChRs by various nicotinic acetylcholine receptor ligands in the presence and absence of an  $\alpha 4\beta 2$  PAM, 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile (Compound 1). In general, these nicotinic ligands are found to be more potent in activating  $\alpha 4\beta 2$  nAChRs in the presence of  $\alpha 4\beta 2$  PAM (Compound 1).

Figure 6A graphically represents the effect of an  $\alpha 4\beta 2$  PAM, 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile (Compound 1), on enhancing the efficacy by 5-[(2R)-azetidin-2-ylmethoxy]-2-chloropyridine (Compound A) in reversing neuropathic pain.

Figure 6B graphically represents the dose dependent effect of an  $\alpha 4\beta 2$  PAM, 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile (Compound 1), on enhancing the neuropathic pain efficacy of 5-[(2R)-azetidin-2-ylmethoxy]-2-chloropyridine (Compound A). An ineffective dose of Compound A (1 nmol/kg) demonstrates effect when combined with various doses of  $\alpha 4\beta 2$  PAM (Compound 1).

Figure 7A shows dose-dependent effects in neuropathic pain of 5-[(2R)-azetidin-2-ylmethoxy]-2-chloropyridine (Compound A) alone,  $\alpha 4\beta 2$  PAM, 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile (Compound 1), alone and a combination of Compound 1 (3.5  $\mu\text{mol/kg}$ ) with various doses of Compound A. An  $\alpha 4\beta 2$  PAM (Compound 1) alone is ineffective. However, in the presence of Compound 1 the dose response curve of Compound A in the Chung model of neuropathic pain shifts to the left.

Figure 7B shows the effects on emesis in ferrets. The effects of 5-[(2R)-azetidin-2-ylmethoxy]-2-chloropyridine (Compound A) alone,  $\alpha 4\beta 2$  PAM, 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile (Compound 1), alone and a combination of Compound 1 (3.5  $\mu\text{mol/kg}$ ) with various doses of Compound A are shown. An  $\alpha 4\beta 2$  PAM (Compound 1) alone does not cause emesis, and does not shift the dose response curve of Compound A in the ferret model of emesis.

Figure 8A and 8B show plasma level analysis in models of neuropathic pain and emesis. The efficacy of Compound A is shifted left-ward as shown in Figure 8A, but no shift in effects on emesis are shown in Figure 8B. The maximal efficacy of Compound A can be realized in neuropathic pain without incidence of emesis, in presence of  $\alpha 4\beta 2$  PAM, 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile (Compound 1). The data demonstrates that the therapeutic window of  $\alpha 4\beta 2$  nAChR agonists is wider in the presence of  $\alpha 4\beta 2$  PAM.

Figure 9 shows the efficacy of a partial agonist, Compound D, in the presence and absence of  $\alpha 4\beta 2$  PAM, 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile (Compound 1). In the example illustrated, Compound D when administered alone is ineffective in relieving pain. When co-dosed with  $\alpha 4\beta 2$  PAM (Compound 1), Compound D demonstrates effect, and the data demonstrate that Compound D provides significant relief of neuropathic pain in rats.

Figure 10 is a graphical representation of specific binding to receptor sites in human brain membranes (fmoles per mg protein) as a function of the concentration of a radioligand [ $^3\text{H}$ ]-3-(5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzotrile ([ $^3\text{H}$ ]-POB, nM).

Figure 11 shows the effects in MIA-induced osteoarthritis pain of 5-[(2R)-azetidin-2-ylmethoxy]-2-chloropyridine (Compound A) alone and a combination of Compound A with an  $\alpha 4\beta 2$  PAM, 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile (Compound 1). In the presence of Compound 1, the dose response curve of Compound A in the MIA-induced osteoarthritis pain model shifts to the left.

Figure 12 shows the effects of 5-[(2R)-azetidin-2-ylmethoxy]-2-chloropyridine (Compound A) alone and a combination of Compound A with an  $\alpha 4\beta 2$  PAM, 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile (Compound 1) on carrageenan-induced acute inflammatory thermal hyperalgesia.

Figure 13 shows the effects of 5-[(2R)-azetidin-2-ylmethoxy]-2-chloropyridine (Compound A) alone and a combination of Compound A with an  $\alpha 4\beta 2$  PAM, 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile (Compound 1) on post-operative pain behaviors.

## DETAILED DESCRIPTION OF THE INVENTION

### Definition of Terms

For a variable that occurs more than one time in any substituent or in the compound of the invention or any other formulae herein, its definition at each occurrence is independent of its definition at every other occurrence. Combinations of substituents are permissible only if such combinations result in stable compounds.

As used throughout this specification and the appended claims, the designation C<sub>x</sub> – C<sub>y</sub>, wherein x and y are integers from 1 to 10 refer to a range of carbon atoms in the hydrocarbon portion of the group which it modifies, for example, the designation "C<sub>1</sub> – C<sub>6</sub> haloalkyl" refers to at least one halogen appended to the parent molecular moiety through an alkyl group having from 1 to 6 carbon atoms.

As used in the specification and the appended claims, unless specified to the contrary, the following terms have the meaning indicated:

The term "acyl hydrazide", as used herein, means a –C(O)NHNH<sub>2</sub> group.

The term "alkenyl", as used herein, means a straight or branched chain hydrocarbon containing from 2 to 10 carbons and containing at least one carbon-carbon double bond formed by the removal of two hydrogens. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, and 3-decenyl.

The term "alkoxy", as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, and hexyloxy.

The term "alkoxyalkoxy", as used herein, means an alkoxy group, as defined herein, appended to the parent molecular moiety through another alkoxy group, as defined herein. Representative examples of alkoxyalkoxy include, but are not limited to, tert-butoxymethoxy, 2-ethoxyethoxy, 2-methoxyethoxy, and methoxymethoxy.

The term "alkoxyalkoxyalkyl", as used herein, means an alkoxyalkoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkoxyalkoxyalkyl include, but are not limited to, tert-butoxymethoxymethyl, ethoxymethoxymethyl, (2-methoxyethoxy)methyl, and 2-(2-methoxyethoxy)ethyl.

The term "alkoxyalkyl", as used herein, means an alkoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkoxyalkyl include, but are not limited to, tert-butoxymethyl, 2-ethoxyethyl, 2-methoxyethyl, and methoxymethyl.

The term "alkoxycarbonyl", as used herein, means an alkoxy group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkoxycarbonyl include, but are not limited to, methoxycarbonyl, ethoxycarbonyl, and tert-butoxycarbonyl.

The term "alkoxycarbonylalkyl", as used herein, means an alkoxycarbonyl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkoxycarbonylalkyl include, but are not limited to, 3-methoxycarbonylpropyl, 4-ethoxycarbonylbutyl, and 2-tert-butoxycarbonylethyl.

5 The term "alkoxycarbonylamino", as used herein, means an alkoxycarbonyl group, as defined herein, appended to the parent molecular moiety through an amino group, as defined herein. Representative examples of alkoxycarbonylamino include, but are not limited to, t-butoxycarbonylamino and methoxycarbonylamino.

10 The term "alkoxycarbonylaminoalkyl", as used herein, means an alkoxycarbonylamino group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkoxycarbonylaminoalkyl include, but are not limited to, t-butoxycarbonylaminomethyl and methoxycarbonylaminoethyl.

15 The term "alkoxysulfonyl", as used herein, means an alkoxy group, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein. Representative examples of alkoxysulfonyl include, but are not limited to, methoxysulfonyl, ethoxysulfonyl and propoxysulfonyl.

20 The term "alkyl", as used herein, means a straight or branched chain hydrocarbon containing from 1 to 10 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, and n-decyl.

25 The term "alkylamino", as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through an amino group, as defined herein. Representative examples of alkylamino include, but are not limited to, methylamino, ethylamino, and t-butylamino.

30 The term "alkylcarbonyl", as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkylcarbonyl include, but are not limited to, acetyl, 1-oxopropyl, 2,2-dimethyl-1-oxopropyl, 1-oxobutyl, and 1-oxopentyl.

The term "alkylcarbonylalkyl", as used herein, means an alkylcarbonyl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkylcarbonylalkyl include, but are not limited to, 2-oxopropyl, 3,3-dimethyl-2-oxopropyl, 3-oxobutyl, and 3-oxopentyl.

The term "alkylcarbonyloxy", as used herein, means an alkylcarbonyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkylcarbonyloxy include, but are not limited to, acetyloxy, ethylcarbonyloxy, and tert-butylcarbonyloxy.

5 The term "alkylcarbonyloxyalkyl", as used herein, means an alkylcarbonyloxy group, as defined herein, appended to the parent molecular moiety through an alkyl group.

The term "alkylene", as used herein, means a divalent group derived from a straight or branched chain hydrocarbon of from 1 to 10 carbon atoms. Representative examples of alkylene include, but are not limited to, -CH<sub>2</sub>-, -CH(CH<sub>3</sub>)-, -C(CH<sub>3</sub>)<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-,  
10 -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, and -CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>-.

The term "alkylsulfinyl", as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through a sulfinyl group, as defined herein. Representative examples of alkylsulfinyl include, but are not limited to, methylsulfinyl and ethylsulfinyl.

15 The term "alkylsulfinylalkyl", as used herein, means an alkylsulfinyl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkylsulfinylalkyl include, but are not limited to, methylsulfinylmethyl and ethylsulfinylmethyl.

The term "alkylsulfonyl", as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein.  
20 Representative examples of alkylsulfonyl include, but are not limited to, methylsulfonyl and ethylsulfonyl.

The term "alkylsulfonylalkyl", as used herein, means an alkylsulfonyl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined  
25 herein. Representative examples of alkylsulfonylalkyl include, but are not limited to, methylsulfonylmethyl and ethylsulfonylmethyl.

The term "alkylthio", as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through a sulfur atom. Representative examples of alkylthio include, but are not limited, methylthio, ethylthio, tert-butylthio, and hexylthio.

30 The term "alkylthioalkyl", as used herein, means an alkylthio group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkylthioalkyl include, but are not limited, methylthiomethyl and 2-(ethylthio)ethyl.

The term "alkynyl", as used herein, means a straight or branched chain hydrocarbon group containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple bond. Representative examples of alkynyl include, but are not limited, to acetylenyl, 1-propynyl, 2-propynyl, 3-butynyl, 2-pentynyl, and 1-butynyl.

5 The term "amino", as used herein, means a  $\text{-NH}_2$  group.

The term "aminoalkyl", as used herein, means at least one amino group, as defined herein, is appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of hydroxyalkyl include, but are not limited to, aminomethyl, 2-aminoethyl, 3-aminopropyl, and 2-ethyl-4-aminoheptyl.

10 The term "amido", as used herein, means an amino ( $\text{H}_2\text{N-}$ ), alkylamino (alkylN(H)-), dialkylamino (alkyl<sub>2</sub>N-), arylamino (arylN(H)-), arylalkylamino (arylalkylN(H)-) or another substituted amine group appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of amido include, but are not limited to, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, and ethylmethylaminocarbonyl.

15 The term "aryl," as used herein, means phenyl, a bicyclic aryl or a tricyclic aryl. The bicyclic aryl is naphthyl, a phenyl fused to a cycloalkyl, or a phenyl fused to a cycloalkenyl. Representative examples of the bicyclic aryl include, but are not limited to, dihydroindenyl, indenyl, naphthyl, dihydronaphthalenyl, and tetrahydronaphthalenyl. The tricyclic aryl is anthracene or phenanthrene, or a bicyclic aryl fused to a cycloalkyl, or a bicyclic aryl fused to a cycloalkenyl, or a bicyclic aryl fused to a phenyl. Representative examples of tricyclic aryl ring include, but are not limited to, azulenyl, dihydroanthracenyl, fluorenyl, and tetrahydrophenanthrenyl.

20 The aryl groups of this invention can be substituted with 0, 1, 2, 3, 4 or 5 substituents independently selected from alkenyl, alkoxy, alkoxyalkoxy, alkoxyalkoxyalkyl, alkoxyalkyl, alkoxyacetyl, alkoxyacetylalkyl, alkyl, alkylacetyl, alkylacetylalkyl, alkylacetyloxy, alkylacetyloxyalkyl, alkylsulfinyl, alkylsulfinylalkyl, alkylsulfonyl, alkylsulfonylalkyl, alkylthio, alkylthioalkyl, alkynyl, arylalkyl, arylalkoxy, aryloxy, carboxy, carboxyalkyl, cyano, cyanoalkyl, formyl, formylalkyl, halogen, haloalkyl, haloalkoxy, hydroxy, hydroxyalkyl, mercapto, nitro,  $\text{-NZ}^1\text{Z}^2$ , and  $(\text{NZ}^3\text{Z}^4)$ carbonyl.

30 The term "arylalkoxy", as used herein, means an aryl group, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein. Representative examples of arylalkoxy include, but are not limited to, 2-phenylethoxy, 3-naphth-2-ylpropoxy, and 5-phenylpentyloxy.

The term "arylalkyl", as used herein, means an aryl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of arylalkyl include, but are not limited to, benzyl, 2-phenylethyl, 3-phenylpropyl, and 2-naphth-2-ylethyl.

5           The term "aryloxy", as used herein, means an aryl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of aryloxy include, but are not limited to, phenoxy, naphthyloxy, 3-bromophenoxy, 4-chlorophenoxy, 4-methylphenoxy, and 3,5-dimethoxyphenoxy.

The term "carbonyl", as used herein, means a -C(O)- group.

10           The term "carboxy", as used herein, means a -CO<sub>2</sub>H group.

The term "carboxyalkyl", as used herein, means a carboxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of carboxyalkyl include, but are not limited to, carboxymethyl, 2-carboxyethyl, and 3-carboxypropyl.

15           The terms "comprise", "comprises" and "comprising", as used herein, are transitional terms, which are synonymous with "including," "containing," or "characterized by," are inclusive or open-ended and do not exclude additional, unrecited elements or method steps.

The term "concurrent administration" refers to administering the  $\alpha 4\beta 2$  receptor ligand to a patient, who has been prescribed (or has consumed) at least one an  $\alpha 4\beta 2$  PAM, at an appropriate time so that the patient's symptoms may subside. This may mean simultaneous administration of an  $\alpha 4\beta 2$  PAM and an  $\alpha 4\beta 2$  receptor ligand, or administration of the medications at different, but appropriate times. Establishing such a proper dosing schedule will be readily apparent to one skilled in the art, such as a physician treating various pain states.

25           The term "cyano", as used herein, means a -CN group.

The term "cyanoalkyl", as used herein, means a cyano group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of cyanoalkyl include, but are not limited to, cyanomethyl, 2-cyanoethyl, and 3-cyanopropyl.

30           The term "cycloalkenyl", as used herein, means a cyclic hydrocarbon containing from 3 to 8 carbons and containing at least one carbon-carbon double bond formed by the removal of two hydrogens. Representative examples of cycloalkenyl include, but are not limited to, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl, 2,4-cyclohexadien-1-yl and 3-cyclopenten-1-yl.



The term "formyl", as used herein, means a -C(O)H group.

The term "formylalkyl", as used herein, means a formyl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of formylalkyl include, but are not limited to, formylmethyl and 2-  
5 formylethyl.

The term "halo" or "halogen", as used herein, means -Cl, -Br, -I or -F.

The term "haloalkoxy", as used herein, means at least one halogen, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein. Representative examples of haloalkoxy include, but are not limited to, chloromethoxy, 2-  
10 fluoroethoxy, trifluoromethoxy, and pentafluoroethoxy.

The term "haloalkyl", as used herein, means at least one halogen, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of haloalkyl include, but are not limited to, chloromethyl, 2-  
15 fluoroethyl, trifluoromethyl, pentafluoroethyl, and 2-chloro-3-fluoropentyl.

The term "haloalkylcarbonyl", as used herein, means a haloalkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of haloalkylcarbonyl include, but are not limited to, trichloromethylcarbonyl and trifluoromethylcarbonyl.  
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The term "heteroaryl", as used herein, means a monocyclic heteroaryl or a bicyclic heteroaryl. The monocyclic heteroaryl is a 5 or 6 membered ring that contains at least one heteroatom selected from the group consisting of nitrogen, oxygen and sulfur. The 5 membered ring contains two double bonds and the 6 membered ring contains three double bonds. The 5 or 6 membered heteroaryl is connected to the parent molecular moiety through any carbon atom or any substitutable nitrogen atom contained within the heteroaryl, provided  
25 that proper valance is maintained. Representative examples of monocyclic heteroaryl include, but are not limited to, furyl, imidazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, oxazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, and triazinyl. The bicyclic heteroaryl consists of a monocyclic heteroaryl fused to a phenyl, or a monocyclic heteroaryl fused to a cycloalkyl, or  
30 a monocyclic heteroaryl fused to a cycloalkenyl, or a monocyclic heteroaryl fused to a monocyclic heteroaryl, or a monocyclic heteroaryl fused to a monocyclic heterocycle. The bicyclic heteroaryl is connected to the parent molecular moiety through any carbon atom or any substitutable nitrogen atom contained within the bicyclic heteroaryl, provided that proper valance is maintained. Representative examples of bicyclic heteroaryl include, but are not



membered monocyclic heterocycle fused to a cycloalkyl, or a 5 or 6 membered monocyclic heterocycle fused to a cycloalkenyl, or a 5 or 6 membered monocyclic heterocycle fused to a monocyclic heterocycle. The bicyclic heterocycle is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the bicyclic heterocycle. Representative examples of bicyclic heterocycle include, but are not limited to, 1,3-benzodioxolyl, 1,3-benzodithiolyl, 2,3-dihydro-1,4-benzodioxinyl, benzodioxolyl, 2,3-dihydro-1-benzofuranyl, 2,3-dihydro-1-benzothieryl, chromenyl and 1,2,3,4-tetrahydroquinolinyl. The tricyclic heterocycle is a bicyclic heterocycle fused to a phenyl, or a bicyclic heterocycle fused to a cycloalkyl, or a bicyclic heterocycle fused to a cycloalkenyl, or a bicyclic heterocycle fused to a monocyclic heterocycle. The tricyclic heterocycle is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the tricyclic heterocycle. Representative examples of tricyclic heterocycle include, but are not limited to, 2,3,4,4a,9,9a-hexahydro-1H-carbazolyl, 5a,6,7,8,9,9a-hexahydrodibenzo[b,d]furanyl, and 5a,6,7,8,9,9a-hexahydrodibenzo[b,d]thienyl.

The heterocycles of this invention are optionally substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkoxyacetyl, alkoxyacetylalkyl, alkoxyacetylalkyl, alkyl, alkylacetyl, alkylacetylalkyl, alkylacetylalkoxy, alkylthio, alkylthioalkyl, alkynyl, carboxy, carboxyalkyl, cyano, cyanoalkyl, formyl, haloalkoxy, haloalkyl, halogen, hydroxy, hydroxyalkyl, nitro, mercapto, oxo,  $-NZ^1Z^2$  and  $(NZ^3Z^4)$ carbonyl.

The term "hydroxy", as used herein, means an -OH group.

The term "hydroxyalkyl", as used herein, means at least one hydroxy group, as defined herein, is appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of hydroxyalkyl include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2,3-dihydroxypentyl, and 2-ethyl-4-hydroxyheptyl.

The term "hydroxy-protecting group" or "O-protecting group" means a substituent which protects hydroxyl groups against undesirable reactions during synthetic procedures. Examples of hydroxy-protecting groups include, but are not limited to, substituted methyl ethers, for example, methoxymethyl, benzyloxymethyl, 2-methoxyethoxymethyl, 2-(trimethylsilyl)-ethoxymethyl, benzyl, and triphenylmethyl; tetrahydropyranyl ethers; substituted ethyl ethers, for example, 2,2,2-trichloroethyl and t-butyl; silyl ethers, for example, trimethylsilyl, t-butyl dimethylsilyl and t-butyl diphenylsilyl; cyclic acetals and

ketals, for example, methylene acetal, acetonide and benzylidene acetal; cyclic ortho esters, for example, methoxymethylene; cyclic carbonates; and cyclic boronates. Commonly used hydroxy-protecting groups are disclosed in T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999).

5           The term "lower alkenyl", as used herein, is a subset of alkenyl, as defined herein, and means an alkenyl group containing from 2 to 4 carbon atoms. Examples of lower alkenyl are ethenyl, propenyl, and butenyl.

10           The term " lower alkoxy", as used herein, is a subset of alkoxy, as defined herein, and means a lower alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom, as defined herein. Representative examples of lower alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, and tert-butoxy.

15           The term "lower alkyl", as used herein, is a subset of alkyl, as defined herein, and means a straight or branched chain hydrocarbon group containing from 1 to 4 carbon atoms. Examples of lower alkyl are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and tert-butyl.

20           The term "lower haloalkoxy", as used herein, is a subset of haloalkoxy, as defined herein, and means a straight or branched chain haloalkoxy group containing from 1 to 4 carbon atoms. Representative examples of lower haloalkoxy include, but are not limited to, trifluoromethoxy, trichloromethoxy, dichloromethoxy, fluoromethoxy, and pentafluoroethoxy.

25           The term "lower haloalkyl", as used herein, is a subset of haloalkyl, as defined herein, and means a straight or branched chain haloalkyl group containing from 1 to 4 carbon atoms. Representative examples of lower haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, dichloromethyl, fluoromethyl, and pentafluoroethyl.

          The term "mammal" includes humans and animals, such as cats, dogs, swine, cattle, horses, and the like.

30           The term "methylenedioxy", as used herein, means a -OCH<sub>2</sub>O- group wherein the oxygen atoms of the methylenedioxy are attached to the parent molecular moiety through two adjacent carbon atoms.

          The term "nitrogen protecting group", as used herein, means those groups intended to protect an amino group against undesirable reactions during synthetic procedures. Preferred nitrogen protecting groups are acetyl, benzoyl, benzyl, benzyloxycarbonyl (Cbz), formyl,

phenylsulfonyl, tert-butoxycarbonyl (Boc), tert-butylacetyl, trifluoroacetyl, and triphenylmethyl (trityl).

The term "mercapto", as used herein, means a -SH group.

The term "nitro", as used herein, means a -NO<sub>2</sub> group.

5 The term "NZ<sup>1</sup>Z<sup>2</sup>", as used herein, means two groups, Z<sup>1</sup> and Z<sup>2</sup>, which are appended to the parent molecular moiety through a nitrogen atom. Z<sup>1</sup> and Z<sup>2</sup> are each independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxy carbonyl, aryl, arylalkyl, and formyl. In certain instances within the invention, Z<sup>1</sup> and Z<sup>2</sup> taken together with the nitrogen atom to which they are attached form a heterocyclic ring. Representative  
10 examples of NZ<sub>1</sub>Z<sub>2</sub> include, but are not limited to, amino, methylamino, acetylamino, acetylmethylamino, phenylamino, benzylamino, azetidiny, pyrrolidinyl and piperidinyl.

The term "NZ<sup>3</sup>Z<sup>4</sup>", as used herein, means two groups, Z<sup>3</sup> and Z<sup>4</sup>, which are appended to the parent molecular moiety through a nitrogen atom. Z<sup>3</sup> and Z<sup>4</sup> are each independently selected from the group consisting of hydrogen, alkyl, aryl and arylalkyl. Representative  
15 examples of NZ<sup>3</sup>Z<sup>4</sup> include, but are not limited to, amino, methylamino, phenylamino and benzylamino.

The term "oxo", as used herein, means a =O moiety.

The term "pain", as used herein, is understood to mean nociceptive pain and neuropathic pain, both chronic and acute pain, including but not limited to, osteoarthritis or  
20 rheumatoid arthritis pain, ocular pain, pains associated with intestinal inflammation, pains associated with cardiac muscle inflammation, pains associated with multiple sclerosis, pains associated with neuritis, pains associated with carcinomas and sarcomas, pains associated with AIDS, pains associated with chemotherapy, amputation pain, trigeminal neuralgia, headaches, such as migraine cephalalgia, or neuropathic pains, such as post-herpes zoster  
25 neuralgia, post-injury pains and post-operative pains.

The term "pharmaceutically acceptable amide," as used herein, refers to those amides, which retain, upon hydrolysis of the amide bond, the biological effectiveness and properties of the carboxylic acid and are not biologically or otherwise undesirable. Pharmaceutically acceptable amides of the invention can be derived from ammonia, primary C<sub>1-6</sub> alkyl amines and secondary C<sub>1-6</sub> dialkyl amines. In the case of secondary amines, the amine can also be in the form of a 5- or 6-membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C<sub>1-3</sub> alkyl primary amides and C<sub>1-2</sub> dialkyl secondary amides are preferred. Amides of the compounds of formulas (I) and (II) can be prepared according to conventional methods. Pharmaceutically acceptable amides can be prepared from compounds containing  
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primary or secondary amine groups by reaction of the compound that contains the amino group with an alkyl anhydride, aryl anhydride, acyl halide, or aroyl halide. In the case of compounds containing carboxylic acid groups, the pharmaceutically acceptable esters are prepared from compounds containing the carboxylic acid groups by reaction of the compound with base such as triethylamine, a dehydrating agent such as dicyclohexyl carbodiimide or carbonyl diimidazole, and an alkyl amine, dialkylamine, for example with methylamine, diethylamine, piperidine. They also can be prepared by reaction of the compound with an acid such as sulfuric acid and an alkylcarboxylic acid such as acetic acid, or with acid and an arylcarboxylic acid such as benzoic acid under dehydrating conditions as with molecular sieves added. The composition can contain a compound of the invention in the form of a pharmaceutically acceptable prodrug.

The term "pharmaceutically acceptable prodrug" or "prodrug" as used herein, represents those prodrugs of the compounds of the invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use. Prodrugs of the invention can be rapidly transformed in vivo to a parent compound of the invention, for example, by hydrolysis in blood. A thorough discussion is provided in Higuchi T., et al., Pro-drugs as Novel Delivery Systems, V. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press (1987).

The term "pharmaceutically acceptable carrier" as used herein, means a non-toxic, solid, semi-solid or liquid filler, diluent, encapsulating material, or formulation auxiliary of any type. Examples of therapeutically suitable excipients include sugars; cellulose and derivatives thereof; oils; glycols; solutions; buffering, coloring, releasing, coating, sweetening, flavoring, and perfuming agents; and the like. These therapeutic compositions can be administered parenterally, intracisternally, orally, rectally, intravenously, or intraperitoneally.

The term "sulfinyl", as used herein, means a -S(O)- group. "

The term "sulfonamide", as used herein means an amino, alkylamino, or dialkylamino group, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein. Representative examples include, but are not limited to, aminosulfonyl, methylaminosulfonyl, and diethylaminosulfonyl.

The term "sulfonyl", as used herein, means a -SO<sub>2</sub>- group.

The term "tautomer", as used herein, means a proton shift from one atom of a compound to another atom of the same compound wherein two or more structurally distinct compounds are in equilibrium with each other.

The term "radiolabel" refers to a compound in which at least one of the atoms is a radioactive atom or radioactive isotope, wherein the radioactive atom or isotope spontaneously emits gamma rays or energetic particles, for example alpha particles or beta particles, or positrons. Examples of such radioactive atoms include, but are not limited to,  $^3\text{H}$  (tritium),  $^{14}\text{C}$ ,  $^{11}\text{C}$ ,  $^{15}\text{O}$ ,  $^{18}\text{F}$ ,  $^{35}\text{S}$ ,  $^{123}\text{I}$ , and  $^{125}\text{I}$ . Compounds suitable for the composition, method, and article of manufacture for the invention are any chemical compounds for which  $\alpha 4\beta 2$  nicotinic receptor activity can be identified.

The term "treatment" or "treating" includes any process, action, application, therapy, or the like, wherein a subject, including human, is provided medical aid with the object of improving the subject's condition, directly or indirectly, or slowing the progression of a condition or disorder in the subject.

Although typically it may be recognized that an asterisk is used to indicate that the exact subunit composition of a receptor is uncertain, for example  $\alpha 4\beta 2^*$  indicates a receptor that contains the  $\alpha 4$  and  $\beta 2$  subunit proteins in combination with other subunits.

It has been found that the efficacy of nicotinic receptor ligands surprisingly can be improved by combining a nicotinic acetylcholine receptor ligand, particularly an  $\alpha 4\beta 2$  receptor ligand (agonist, partial agonist), with a nicotinic acetylcholine receptor  $\alpha 4\beta 2$  subtype selective positive allosteric modulator (PAM). Such combinations are highly efficient for improving the efficacy of  $\alpha 4\beta 2$  ligand for treatment of pain and other disease indications such as cognitive deficits when compared to administration of an  $\alpha 4\beta 2$  receptor ligand alone.

#### Nicotinic Acetylcholine Subtype $\alpha 4\beta 2$ Receptor Ligands

Nicotinic acetylcholine subtype  $\alpha 4\beta 2$  receptor ligands modulate the function by altering the activity of the receptor. Suitable compounds for use in the methods and compositions of the present invention can also be partial agonists that partially block or partially activate the  $\alpha 4\beta 2$  receptor or agonists that activate the receptor. Nicotinic acetylcholine receptor  $\alpha 4\beta 2$  receptor ligands suitable for the invention can include full agonists or partial agonists of various structural classes. Compounds modulating activity of

nicotinic acetylcholine receptor  $\alpha 4\beta 2$  subtype are suitable for the invention regardless of the manner in which they interact with the receptor.

One manner for characterizing  $\alpha 4\beta 2$  receptor ligands is by a binding assay. [ $^3\text{H}$ ]-Cytisine binding values (“ $K_i$  Cyt”) of compounds of the invention ranged from about 0.001 nanomolar to greater than 100 micromolar. Preferred compounds for the composition demonstrate binding values of from about 0.001 nanomolar to 10 micromolar. The [ $^3\text{H}$ ]-cytisine binding assays have been well reported; however, further details for carrying out the assays can be obtained in International Publication No. WO 99/32480; U.S. Patent Nos. 5,948,793 and 5,914,328; WO 2004/018607; U.S. Patent No. 6,809,105; WO 00/71534; and U.S. Patent No. 6,833,370.

Accordingly,  $\alpha 4\beta 2$  receptor ligands suitable for the invention can be compounds of various chemical classes. Particularly, some examples of  $\alpha 4\beta 2$  receptor ligands suitable for the invention include, but are not limited to heterocyclic ether derivatives (see, for example, International Publication No. WO 99/32480, published July 1, 1999; U.S. Patent No. 5,948,793, issued September 7, 1999, and U.S. Patent No 5,914,328, issued June 22, 1999); N-substituted diazabicyclic derivatives (see for example International Publication No. WO 2004/0186107, published September 23, 2004, and U.S. Patent No. 6,809,105, issued October 26, 2004); heterocyclic substituted amino azacycles (see for example, International Publication No. WO 00/71534, published November 30, 2000, and U.S. Patent No. 6,833,370, issued December 21, 2004); all of which are hereby incorporated by reference in their entirety. Further description and methods for preparing the compounds have been reported in the patents, patent publications, and international patent publications cited.

Additional examples of  $\alpha 4\beta 2$  receptor ligands suitable for the invention include, but are not limited to aryl-fused azapolycyclic compounds (see for example, International Publication No. WO 2001062736, published August 30, 2001); aryl-substituted olefinic amine compounds (see for example, International Publication Nos. WO 9965876, published December 23, 1999, and WO 00/75110, published December 14, 2000); pyridopyranoazepine derivatives (see for example, US Patent No. 6,538,003, published March 25, 2003); benzylidene- and cinnamylidene- anabaseines (see for examples, International Publication No. WO 99/10338, published March 4, 1999); and 3-pyridoxylalkyl heterocyclic ether compounds (see for example, International Publication No. WO 96/040682, published December 19, 1996); all of which are hereby incorporated by reference in their entirety.

Further description and methods for preparing the compounds have been reported in the patents and international patent publications cited.

Other compounds reported as demonstrating  $\alpha 4\beta 2$  ligands include, but are not limited to, TC-1734 (ispronicline), GTS-21, 4-hydroxy-GTS-21, TC-5619, TC-2696, dianicline and varenicline, which are all described in the publicly available literature.

Specific examples of compounds contemplated for the  $\alpha 4\beta 2$  receptor ligands include, but are not limited to,

5-[(2R)-azetidin-2-ylmethoxy]-2-chloropyridine;

(3R)-1-pyridin-3-ylpyrrolidin-3-amine;

2-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine;

3-(5,6-dichloro-pyridin-3-yl)-1S,5S-3,6-diazabicyclo[3.2.0]heptane;

(R,R)-1-(pyridin-3-yl)octahydro-pyrrolo[3,4-b]pyrrole;

6,10-methano-6H-pyrazino[2,3-h][3]benzazepine;

7,8,9,10-tetrahydro-(2S,4E)-N-methyl-5-(5-isopropoxy-3-pyridyl)-4-penten-2-amine;

(2S,4E)-N-methyl-5-(5-methoxy-3-pyridyl)-4-penten-2-amine;

(2S,4E)-N-methyl-5-(5-ethoxy-3-pyridyl)-4-penten-2-amine;

(2S,4E)-N-methyl-3-pyrimidine-4-penten-2-amine;

(5aS,8S,10aR)-5a,6,9,10-tetrahydro-7H,11H-8,10a-

methanopyrido[2',3':5,6]pyrano[2,3-d]azepine;

3-[1-(2,4-dimethoxy-phenyl)-meth-(E)-ylidene]-3,4,5,6-tetrahydro-[2,3']bipyridinyl;

and

3-[1-(2-methoxy-4-hydroxyphenyl)-meth-(E)-ylidene]-3,4,5,6-tetrahydro-[2,3']bipyridinyl;

or pharmaceutically acceptable salts thereof.

#### Nicotinic Acetylcholine Subtype $\alpha 4\beta 2$ Receptor Positive Allosteric Modulators

Positive allosteric modulators (PAMs) are compounds that potentiate receptor responses to acetylcholine without themselves triggering receptor activation or desensitization, or either, of the receptor.

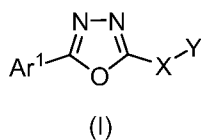
One manner for characterizing  $\alpha 4\beta 2$  positive allosteric modulator activity is by characterization in human HEK cells expressing the human nicotinic acetylcholine receptor subtype  $\alpha 4\beta 2$ , particularly by use of Fluorescent Image Plate Reader technology. Such assay has been reported and further details for carrying out the assays can be obtained in

International Publication Nos. WO 2006/114400, published November 2, 2006. Another method to identify and characterize allosteric modulator activity is by expressing the  $\alpha 4\beta 2$  subunits in *Xenopus* oocytes or cell lines, and by measuring effects on ligand-evoked current responses as previously described (Curtis L, et al., *Molecular Pharmacology*, 61: 127-135, 2002).

Steroid hormones represent a family of molecules with varying modulatory effects on nAChRs as well as other members of the LGIC superfamily. For example, positive allosteric modulation of human  $\alpha 4\beta 2$  nAChRs expressed either in *Xenopus* oocytes or in human embryonic kidney cells was reported with 17  $\beta$ -estradiol (Curtis L, et al., *Molecular Pharmacology*, 61: 127-135, 2002). Examples of compounds reported as selective  $\alpha 4\beta 2$  positive allosteric modulators are oxadiazole derivatives, for example as described in WO 2006/114400.

Another suitable  $\alpha 4\beta 2$  positive allosteric modulator is 3,5-diphenylisoxazole, which is commercially available from Sigma Aldrich, St. Louis, Missouri, USA.

Other suitable examples of  $\alpha 4\beta 2$  positive allosteric modulators include, but are not limited to, oxadiazole derivatives. Suitable oxadiazole derivatives can include 1,2,4-oxadiazole derivatives and 1,3,4-oxadiazole derivatives. Examples of 1,3,4-oxadiazole derivatives are described in co-pending U.S. Patent Application No. 11/953,590, filed on December 10, 2007, wherein the methods of preparation disclosed are incorporated by reference herein. Such compounds have the formula (I):



or are pharmaceutically acceptable salts and prodrugs thereof, wherein:

X is a bond, O, NR<sup>1</sup>, S, or C<sub>1</sub>-C<sub>3</sub> alkylene;

Y represents a monocyclic aryl, cycloalkyl, heterocycle, or heteroaryl group;

Ar<sup>1</sup> represents a monocyclic aryl or a heteroaryl group; and

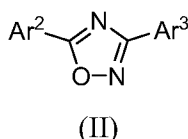
R<sup>1</sup> is hydrogen, alkyl, haloalkyl or arylalkyl.

X is selected from a bond, O, NR<sup>1</sup>, S, or C<sub>1</sub>-C<sub>3</sub> alkylene, wherein R<sup>1</sup> is selected from hydrogen, alkyl, haloalkyl, and arylalkyl. Preferably, X is a bond. Preferably, R<sup>1</sup> is hydrogen or alkyl.



Other suitable examples of compounds reported as  $\alpha 4\beta 2$  positive allosteric modulators are oxadiazole derivatives, for example as described in WO 2006/114400, published November 2, 2006. Further examples of oxadiazole compounds that are suitable as  $\alpha 4\beta 2$  positive allosteric modulators are also provided in WO 02/100826, published December 19, 2002.

Yet other suitable examples of  $\alpha 4\beta 2$  positive allosteric modulators are described in co-pending U.S. Patent Application No. 12/134,678, filed on June 6, 2008, wherein the methods of preparation disclosed are incorporated by reference herein. Such compounds have the formula (II):



or are pharmaceutically acceptable salts and prodrugs thereof, wherein:

$\text{Ar}^2$  is aryl or heteroaryl, wherein the aryl or heteroaryl is substituted or unsubstituted, and, when substituted, the aryl or heteroaryl is substituted with 0, 1, 2, 3, or 4 substituents selected from halo,  $\text{C}_1\text{-C}_6$  haloalkyl,  $\text{C}_6\text{-C}_{10}$  aryl,  $\text{C}_4\text{-C}_7$  cycloalkyl,  $\text{C}_2\text{-C}_6$  alkenyl,  $\text{C}_2\text{-C}_6$  alkynyl,  $\text{C}_5\text{-C}_{10}$  heteroaryl,  $\text{C}_4\text{-C}_{10}$  heterocycle,  $\text{C}_1\text{-C}_6$  alkyl,  $-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{NHC(O)O}-(\text{C}_1\text{-C}_6 \text{ alkyl})$ ,  $\text{C}_1\text{-C}_6$  hydroxyalkyl,  $\text{C}_1\text{-C}_6$  alkylcarbonyl, amino, hydroxyl, haloalkyl- $\text{C(O)-}$ , haloalkyl- $\text{SO}_2\text{-}$ , alkyl- $\text{SO}_2\text{-}$ ,  $-\text{SO}_2\text{NH}_2$ ,  $-\text{SO}_2\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$ ,  $-\text{SO}_2\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})_2$ , cyano, nitro,  $\text{C}_1\text{-C}_6$  acylamino,  $\text{C}_1\text{-C}_6$  alkoxy,  $-\text{C(O)NH}_2$ ,  $-\text{C(O)O}-(\text{C}_1\text{-C}_6 \text{ alkyl})$ , and carboxy; and

$\text{Ar}^3$  is aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted, and, when substituted, the aryl or heteroaryl is substituted with a substituent selected from halo,  $\text{C}_1\text{-C}_6$  haloalkyl,  $\text{C}_6\text{-C}_{10}$  aryl,  $\text{C}_4\text{-C}_7$  cycloalkyl,  $\text{C}_2\text{-C}_6$  alkenyl,  $\text{C}_2\text{-C}_6$  alkynyl,  $\text{C}_5\text{-C}_{10}$  heteroaryl,  $\text{C}_1\text{-C}_6$  alkyl,  $\text{C}_1\text{-C}_6$  hydroxyalkyl, amino, hydroxyl, haloalkyl- $\text{SO}_2\text{-}$ , cyano, nitro,  $\text{C}_1\text{-C}_6$  acylamino,  $\text{C}_1\text{-C}_6$  alkoxy,  $-\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})_2$ , and carboxy.

In one embodiment, suitable 3,5-disubstituted-1,2,4-oxadiazole derivatives can have the formula (I) wherein  $\text{Ar}^2$  is substituted monocyclic aryl or monocyclic heteroaryl, which can be substituted or unsubstituted, and  $\text{Ar}^3$  is substituted monocyclic aryl or heteroaryl, which can be substituted or unsubstituted. When the aryl or heteroaryl group for  $\text{Ar}^2$  is substituted the substituent is selected from halo,  $\text{C}_1\text{-C}_6$  haloalkyl,  $\text{C}_6\text{-C}_{10}$  aryl,  $\text{C}_4\text{-C}_7$  cycloalkyl,  $\text{C}_2\text{-C}_6$  alkenyl,  $\text{C}_2\text{-C}_6$  alkynyl,  $\text{C}_5\text{-C}_{10}$  heteroaryl,  $\text{C}_4\text{-C}_{10}$  heterocycle,  $\text{C}_1\text{-C}_6$  alkyl,  $-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{NHC(O)O}-(\text{C}_1\text{-C}_6 \text{ alkyl})$ ,  $\text{C}_1\text{-C}_6$  hydroxyalkyl,  $\text{C}_1\text{-C}_6$  alkylcarbonyl, amino, hydroxyl, haloalkyl- $\text{C(O)-}$ , haloalkyl- $\text{SO}_2\text{-}$ , alkyl- $\text{SO}_2\text{-}$ ,  $-\text{SO}_2\text{NH}_2$ ,  $-\text{SO}_2\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$ , -

SO<sub>2</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, cyano, nitro, C<sub>1</sub>-C<sub>6</sub> acylamino, C<sub>1</sub>-C<sub>6</sub> alkoxy, -C(O)NH<sub>2</sub>, -C(O)O-(C<sub>1</sub>-C<sub>6</sub> alkyl), and carboxy. When the aryl or heteroaryl group for Ar<sup>3</sup> is substituted the substituent is selected from halo, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>6</sub>-C<sub>10</sub> aryl, C<sub>4</sub>-C<sub>7</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>5</sub>-C<sub>10</sub> heteroaryl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, amino, hydroxyl, haloalkyl-SO<sub>2</sub>,  
 5 cyano, nitro, C<sub>1</sub>-C<sub>6</sub> acylamino, C<sub>1</sub>-C<sub>6</sub> alkoxy, -N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, and carboxy. Preferred for monocyclic heteroaryl are pyridine-3-yl, pyridine-4-yl, and pyridine-2(1H)-one.

In another embodiment, suitable 3,5-disubstituted-1,2,4-oxadiazole derivatives can have the formula (II) wherein Ar<sup>2</sup> is pyridinyl, which can be substituted or unsubstituted, or substituted phenyl; and Ar<sup>3</sup> is pyridinyl, which can be substituted or  
 10 unsubstituted, or substituted phenyl. The pyridinyl group, when substituted, is substituted with fluoro. The phenyl group is substituted with cyano or halo. It is preferred that the pyridinyl group for Ar<sup>2</sup> or Ar<sup>3</sup> is pyridin-3-yl. The preferred phenyl group is substituted with fluoro, sulfonamide or cyano, and preferably cyano.

Specific examples of  $\alpha$ 4 $\beta$ 2 positive allosteric modulators are, for example, 3,5-  
 15 disubstituted-1,2,4-oxadiazole derivatives, such as:

3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile;  
 3,5-di(pyridin-3-yl)-1,2,4-oxadiazole;  
 3-(5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzotrile;  
 3-(5-(6-fluoropyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzotrile;  
 20 5-(5-bromopyridin-3-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 3-(pyridin-3-yl)-5-(3-(trifluoromethylsulfonyl)phenyl)-1,2,4-oxadiazole;  
 3-(3-(6-methylpyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile;  
 5-(5-(pyrrol-1-yl)pyridin-3-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 5-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)pyridin-3-ol;  
 25 5-(3,4-difluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 5-(2,3-difluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 5-(pyrazin-2-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 5-(3,5-difluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 5-(2,3,5-trifluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 30 5-(2,4,5-trifluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 5-(2,5-difluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 5-(4-chloro-2,5-difluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 5-(5-methylpyrazin-2-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;

- 4-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile;  
2,3,6-trifluoro-5-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenol;  
2-fluoro-5-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenol;  
2-fluoro-4-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenol;  
5 5-(3-chloro-4-fluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
5-(3,4-dichlorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
2-nitro-5-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenol;  
5-(2,3,6-trifluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
2,2,2-trifluoro-1-(4-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenyl)ethanone;  
10 5-(3-fluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
5-(4-fluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
5-(2-fluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
3-fluoro-5-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile;  
3-(2,3-difluorophenyl)-5-(pyridin-3-yl)-1,2,4-oxadiazole;  
15 3-(3,4-difluorophenyl)-5-(pyridin-3-yl)-1,2,4-oxadiazole;  
5-(2,6-difluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzenesulfonamide;  
5-(2,4-difluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
5-(2,3,4-trifluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
20 5-(3,4,5-trifluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
5-(4-chloro-3-fluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
5-(3-nitrophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
5-(3-(methylsulfonyl)phenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
3-(2-chloropyridin-4-yl)-5-(pyridin-3-yl)-1,2,4-oxadiazole;  
25 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzamide;  
4-(5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one;  
*tert*-butyl 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzoate;  
2-amino-5-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenol;  
*N,N*-dimethyl-4-(5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)pyridin-2-amine;  
30 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzoic acid;  
5-(3-(1H-tetrazol-5-yl)phenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
*N,N*-diethyl-3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzenesulfonamide;  
2-fluoro-5-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile;  
3-(3-(1H-tetrazol-5-yl)phenyl)-5-(pyridin-3-yl)-1,2,4-oxadiazole;

- 3-(6-chloropyridin-3-yl)-5-(pyridin-3-yl)-1,2,4-oxadiazole;  
 5-(6-chloropyridin-3-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 5-(5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one;  
 5-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)pyridin-2(1H)-one;  
 5 N-methyl-3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzenesulfonamide;  
 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)aniline;  
 (3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenyl)methanamine;  
 5-(2-chloropyridin-4-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 4-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)pyridin-2(1H)-one;  
 10 tert-butyl 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzylcarbamate;  
 5-(3-bromophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 1-(3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenyl)pyrrolidin-2-one;  
*tert*-butyl 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenylcarbamate;  
 N,N-dimethyl-1-(3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenyl)methanamine;  
 15 5-(3-(piperazin-1-yl)phenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 1-(3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenyl)ethanone;  
 3-(6-chloropyridin-3-yl)-5-(2,3-difluorophenyl)-1,2,4-oxadiazole;  
 3-(6-chloropyridin-3-yl)-5-(3,4-difluorophenyl)-1,2,4-oxadiazole;  
 (*R*)-3-(pyridin-3-yl)-5-(3-(pyrrolidin-2-yl)phenyl)-1,2,4-oxadiazole;  
 20 5-(3-(1H-pyrazol-3-yl)phenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 1-(3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenyl)ethanol;  
 3-(3-(6-chloropyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile;  
 3-(4-fluorophenyl)-5-(pyridin-3-yl)-1,2,4-oxadiazole;  
 3-(5-(6-chloropyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzotrile;  
 25 3-(5-(2-fluoropyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzotrile, and  
 3-fluoro-5-(5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzotrile;  
 or pharmaceutically acceptable salts thereof.

Other specific examples of  $\alpha 4\beta 2$  positive allosteric modulators are, for example, 2,5-  
 30 disubstituted-1,3,4-oxadiazole derivatives, such as:

- 2-(imidazo[1,5-a]pyridin-6-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole  
 2,5-di(pyridin-3-yl)-1,3,4-oxadiazole;  
 2-(5-bromopyridin-3-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;

- 2-(pyridin-3-yl)-5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazole;  
2-(pyridin-3-yl)-5-*o*-tolyl-1,3,4-oxadiazole;  
2-(pyridin-3-yl)-5-*m*-tolyl-1,3,4-oxadiazole;  
2-(pyridin-3-yl)-5-*p*-tolyl-1,3,4-oxadiazole;  
5 2-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)phenol;  
3-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)phenol;  
4-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)phenol;  
2-(3-methoxyphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(4-methoxyphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
10 2-(2-fluorophenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(3-fluorophenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(4-fluorophenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(2-chlorophenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(3-chlorophenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
15 2-(4-chlorophenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(2-bromophenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(3-bromophenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(4-bromophenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
3-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)benzotrile;  
20 4-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)benzotrile;  
*N,N*-dimethyl-3-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)aniline;  
*N,N*-dimethyl-4-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)aniline;  
2-(pyridin-3-yl)-5-(3-(trifluoromethyl)phenyl)-1,3,4-oxadiazole;  
2-(pyridin-3-yl)-5-(3-(trifluoromethoxy)phenyl)-1,3,4-oxadiazole;  
25 2-(4-phenoxyphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(4-(benzyloxy)phenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(3,4-dimethylphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(3,5-dimethylphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(2,5-dimethylphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
30 2-(2,4-dimethylphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(3,4-dimethylphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(2,3-dimethoxyphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(2,4-dimethoxyphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(2,5-dimethoxyphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;

- 2-(2,4-dimethoxyphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(3,5-dimethoxyphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(benzo[d][1,3]dioxol-5-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(pyridin-3-yl)-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole;  
5 2-(3,4-dichlorophenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(2,4-dichlorophenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(2,5-dichlorophenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(3,4-dichlorophenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
5-methyl-2-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)phenol;  
10 2-methyl-5-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)phenol;  
2-(3-fluoro-2-methylphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(5-fluoro-2-methylphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(3-fluoro-4-methylphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(2,3-difluorophenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
15 2-(2,4-difluorophenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(2,5-difluorophenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(3,5-difluorophenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
1-(4-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)phenyl)ethanone;  
2-(4-isopropylphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
20 2-(3-methoxy-4-methylphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(4-ethoxyphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(4-(methylthio)phenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(3-fluoro-4-methoxyphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(naphthalen-1-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
25 2-(naphthalen-2-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
4-chloro-2-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)phenol;  
2-(4-tert-butylphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
*N*-(4-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)phenyl)acetamide;  
2-(4-propoxyphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
30 2-(4-isopropoxyphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(5-chloro-2-methoxyphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
2-(4-fluoronaphthalen-1-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
*N,N*-diethyl-4-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)aniline;  
2-(4-butoxyphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;

- 2-(2-methoxy-4-(methylthio)phenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
 2-(4-(methylsulfonyl)phenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
 2-(2-chloro-5-(methylthio)phenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
 2-(2-fluoro-5-(trifluoromethyl)phenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
 5 2-(2-chloro-5-(trifluoromethyl)phenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
 2-(2-phenethylphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
 2-(2-bromo-5-methoxyphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
 2-(5-bromo-2-chlorophenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
 2-(2-iodophenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
 10 2-(3-iodophenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
 2-(4-iodophenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
 2-(pyridin-3-yl)-5-(pyrimidin-5-yl)-1,3,4-oxadiazole;  
 2-(5-methylpyrazin-2-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
 2-(2-chloro-6-methylpyridin-3-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
 15 2-(2-methyl-6-(trifluoromethyl)pyridin-3-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
 2-(2-(ethylthio)pyridin-3-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
 2-(2,6-dimethoxypyridin-3-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
 2-(2-(methylthio)pyridin-3-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
 5-chloro-3-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)pyridin-2-ol;  
 20 2-(2,6-dichloro-5-fluoropyridin-3-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
 2-(2,5-dichloropyridin-3-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
 2-(6-chloropyridin-3-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
 2-(2,6-dichloropyridin-3-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
 2-(2-chloropyridin-3-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
 25 2-(pyridin-3-yl)-5-(quinolin-3-yl)-1,3,4-oxadiazole; and  
 2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;  
 or pharmaceutically acceptable salts thereof.

Many other examples of  $\alpha 4\beta 2$  positive allosteric modulators are reported in the  
 30 literature and can be used in the method of treating pain of the present invention. Such  
 examples include, but are not limited to, isoxazole derivatives. Examples of isoxazole  
 derivatives are described in co-pending U.S. Patent Application No. 61/058,735, filed on

June 4, 2008, wherein the compounds and methods of preparation disclosed are incorporated by reference herein.

Various embodiments of the invention described herein include, but are not limited to, pharmaceutically acceptable salts, amides, esters and prodrugs thereof.

5 Compound names are assigned by using Struct=Name naming algorithm, which is part of the CHEMDRAW® ULTRA v. 9.0.7 software suite.

Compounds of the present application may exist as stereoisomers wherein, asymmetric or chiral centers are present. These stereoisomers are "R" or "S" depending on the configuration of substituents around the chiral carbon atom. The terms "R" and "S" used  
10 herein are configurations as defined in IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem., 1976, 45: 13-30.

The present application contemplates various stereoisomers and mixtures thereof and these are specifically included within the scope of this application. Stereoisomers include enantiomers and diastereomers, and mixtures of enantiomers or diastereomers. Individual  
15 stereoisomers of compounds of the present application may be prepared synthetically from commercially available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution which is well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of  
20 diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic columns.

Geometric isomers can exist in the present compounds. The invention contemplates the various geometric isomers and mixtures thereof resulting from the disposition of  
25 substituents around a carbon-carbon double bond, a carbon nitrogen double bond, a cycloalkyl group, or a heterocycloalkyl group. Substituents around a carbon-carbon or carbon-nitrogen double bond are designated as being of Z or E configuration and substituents around a cycloalkyl or heterocycloalkyl are designated as being of cis or trans configuration.

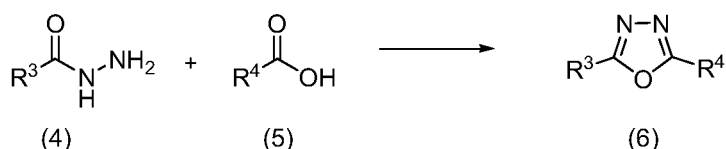
Within the present invention it is to be understood that compounds disclosed herein  
30 can exhibit the phenomenon of tautomerism. Thus, when the formulae drawings within this specification represent one of the possible tautomeric or stereoisomeric forms, it is to be understood that the invention encompasses any tautomeric or stereoisomeric form, and mixtures thereof, and is not to be limited merely to any one tautomeric or stereoisomeric form utilized within the naming of the compounds or formulae drawings.



As shown in Scheme 1, compounds of formula (II), wherein Ar<sup>2</sup> and Ar<sup>3</sup>, are as defined in formula (II) above, can be prepared as described in Scheme 1. Aryl or heteroaryl compounds of general formula (1), can be treated with formula (2) with heat in a solvent including, but not limited to pyridine, to provide of general formula (II).

5

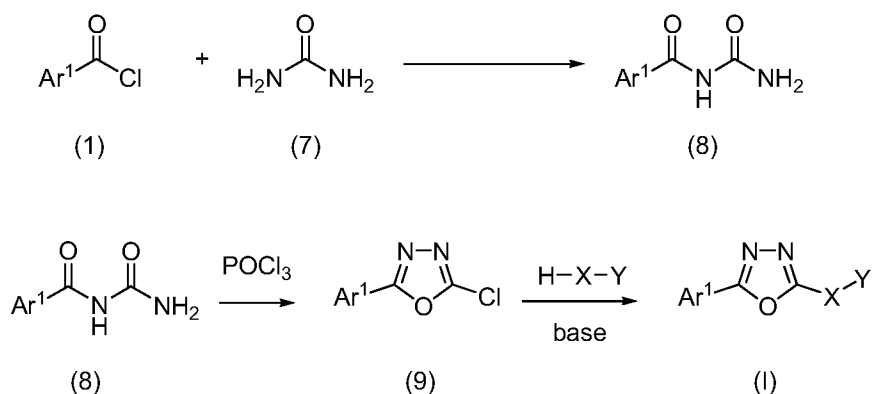
Scheme 2



As shown in Scheme 2, compounds of formula (4) can be reacted with compounds of formula (5) in POCl<sub>3</sub> at temperatures from 40-100 °C over 1-24 hours to provide compounds of formula (6); wherein R<sup>3</sup> is Ar<sup>1</sup> and R<sup>4</sup> is Y, or R<sup>3</sup> is Y and R<sup>4</sup> is Ar<sup>1</sup>. Alternatively, compounds of formula (4) can be reacted with compounds of formula (5) in the presence of triphenylphosphine, which may optionally be polymer bound, and trichloroacetonitrile in acetonitrile. The mixture may be heated in a microwave oven at 100-175 °C for 5-30 minutes as described by Wang, Y.; Sauer, D.R.; Djuric, S.W. *Tetrahedron. Lett.* 2006, 47, 105-108. Another alternative includes combining compounds of formula (4) and compounds of formula (5) in a solvent such as methylene chloride in the presence of 2-chloro-1,3-dimethylimidazolium chloride and a base such as triethylamine at 15-35 °C for 10-120 hours as described by Isobe, T.; Ishikawa, T. *J. Org. Chem.* 1999, 64, 6989-6992.

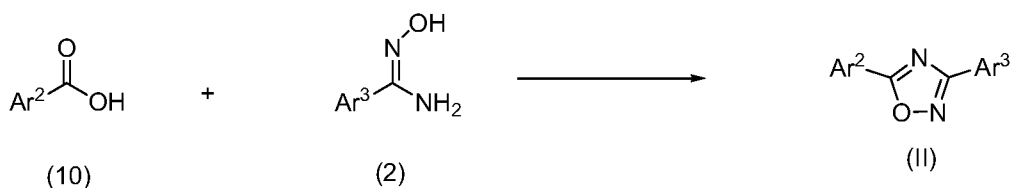
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Scheme 3



As shown in Scheme 3, compounds of formula (1) can be reacted with urea (7) in a solvent such as dichloromethane in the presence of a base such as triethylamine at 25-40 °C

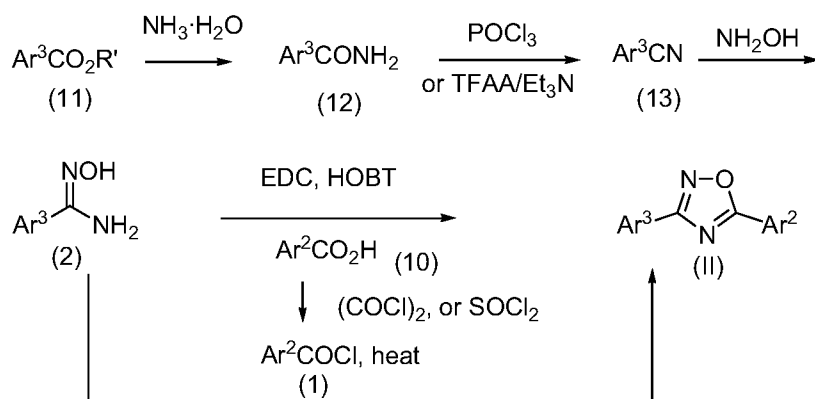
for 1-12 hours to provide compounds of formula (8) as described in Sobol, E.; Bialer, M.; Yagen, B. J. Med. Chem. 2004, 47, 4316-4326. Alternatively, compounds of formula (1) and (7) may be combined in pyridine at 20-110 °C for 1-24 hours to provide compounds of formula (8). Compounds of formula (8) can be treated with POCl<sub>3</sub> at 25-100 °C for 1-24  
5 hours to provide compounds of formula (9). Compounds of formula (9) can be reacted with H-X-Y in the presence of a base such as lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, potassium *t*-butoxide, sodium hydride, potassium carbonate, sodium carbonate, cesium or carbonate in a solvent such as tetrahydrofuran, 1-methyl-2-pyrrolidinone, dimethyl sulfoxide, or acetonitrile at temperatures  
10 from -20 °C to 150 °C over 1-48 hours to provide compounds of formula (I).

Scheme 4

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As shown in Scheme 4, compounds of formula (II), wherein Ar<sup>2</sup> and Ar<sup>3</sup>, are as defined in formula (II), can be prepared as described in Scheme 4. Aryl or heteroaryl compounds of general formula (10), can be treated with compounds of formula (2) in the presence of a coupling agent such as N-(3-methylaminopropyl)-N'-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole with heat in a solvent including, but not limited to  
20 dimethylformamide, to provide compounds of general formula (II).

Scheme 5

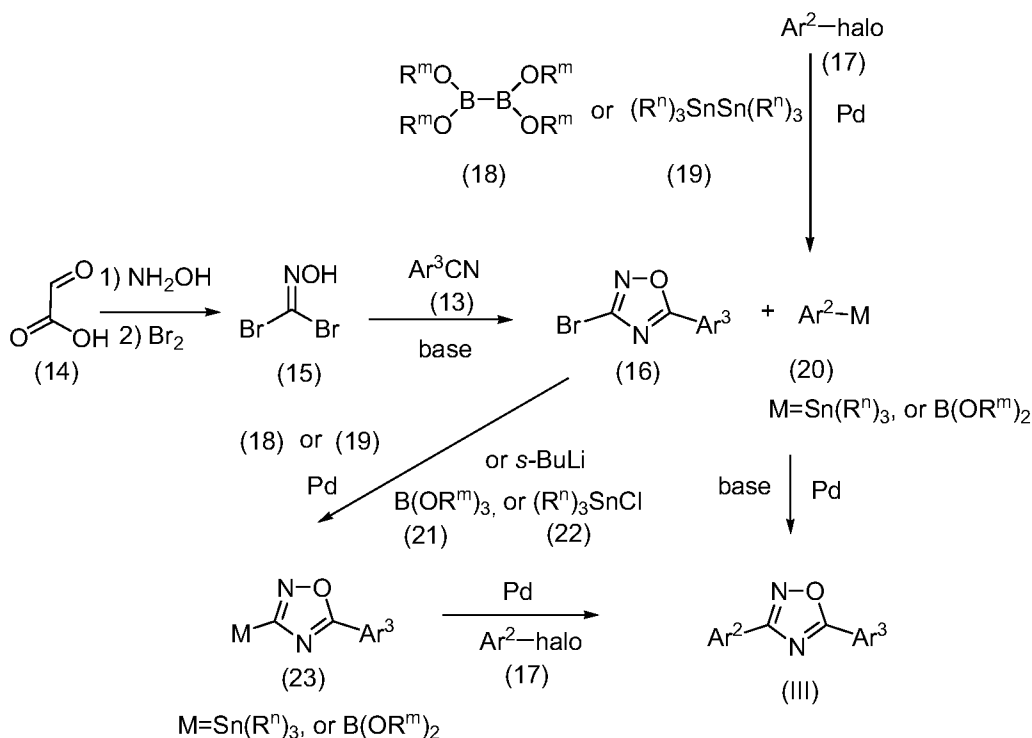


5

As shown in Scheme 5, compounds of formula (II), wherein Ar<sup>2</sup> and Ar<sup>3</sup>, are as previously defined, can be prepared as described in Scheme 5. Compounds of formula (13), which can be either obtained from a commercial source or prepared from compounds of formula (11). Amides of formula (12) can be prepared by reacting compounds of formula (11) with ammonium hydroxide. Subsequent dehydration of compound of formula (12) with a dehydrating agent, such as but not limited to phosphorous oxychloride or trifluoroacetic anhydride (TFAA)/triethylamine provide compounds of formula (13). Compounds of formula (13) can be reacted with hydroxylamine to give compounds of formula (2). Compounds of formula (2) react with an aromatic carboxylic acids of formula (10) in the presence of a coupling agent, such as but not limited to N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC)/1-hydroxybenzotriazole (HOBT), in dimethylformamide at 80-120 °C to give compounds of formula (II). Alternatively, compounds of formula (II) can also be prepared by heating a mixture of compounds of formula (2) and compound of formula (1) which can be obtained from either a commercial source or by the treatment of compound of formula (10) with a chlorinating agent, such as oxalyl chloride or thionyl chloride, in a solvent such as but not limited to pyridine or THF at 60-110 °C.

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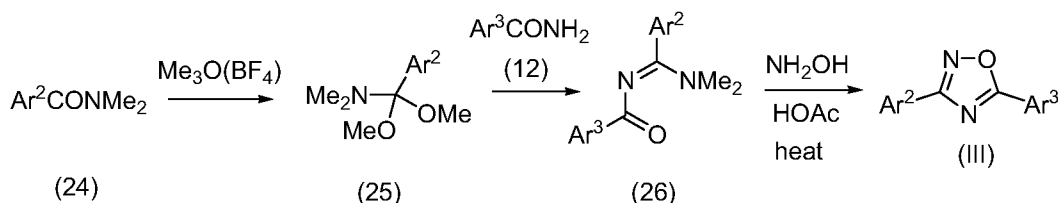
Scheme 6



Compounds of formula (III), wherein Ar<sup>2</sup> and Ar<sup>3</sup> are as defined in formulas (II), can be prepared as described in Scheme 6. Compounds of formula (14) can be first reacted with hydroxylamine at ambient temperature and then treated with bromine in dichloromethane at temperatures from 0-20 °C to provide compounds of formula (15) as described by Berrier, J. V. and Umarvadia, A. S. in *EP0979814*. The compounds of formula (15) reacts with compounds of formula (13) in the presence a base, such as but not limited to triethylamine, Na<sub>2</sub>CO<sub>3</sub> and K<sub>2</sub>CO<sub>3</sub>, in a solvent, such as toluene, at temperature ranging 80-110 °C over 10-40 hours to provide compounds of formula (16) as described by Humphrey, G. R.; Wright, S. H. B. in *J. Heterocyclic Chem.* (1989, 26, 23-24). Compounds of formula (17), wherein halo is chloro, bromo or iodo, when treated with an organoboranes of formula (18) or ditiin compounds of formulas (19), such as bis(pinacolato)diboron or hexmethylditin, respectively, wherein R<sup>m</sup> or R<sup>n</sup> are hydrogen, alkyl or aryl, in the presence of a palladium catalyst, such as, but not limited to Pd(OAc)<sub>2</sub>, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>, PdCl<sub>2</sub>(dppf), Pd<sub>2</sub>(dba)<sub>3</sub> provide the corresponding tin or boronic acid or boronic esters of formula (20), wherein M is -Sn-(R<sup>n</sup>)<sub>3</sub> or -B(OR<sup>m</sup>)<sub>2</sub>. Compounds of formula (16) can be reacted with compounds of formula (20) in the presence of a palladium catalyst, such as, but not limited to Pd(OAc)<sub>2</sub>, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>, PdCl<sub>2</sub>(dppf), Pd<sub>2</sub>(dba)<sub>3</sub>, and a base, such as but not limited to CsF, Na<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub> and K<sub>3</sub>PO<sub>4</sub>, will provide compounds of formula (III). Alternatively, compounds of

formula (16) when treated with organoboranes of formula (18) or ditiin compounds of formulas (19), such as bis(pinacolato)diboron or hexmethylditin, respectively, in the presence of a palladium catalyst provide organotin compounds, organoboronic acids or organoboronic esters compounds of formula (23), wherein M is  $-\text{Sn}-(\text{R}^n)_3$  or  $-\text{B}(\text{OR}^m)_2$ . Compounds of formula (23) can also be prepared by the initial treatment of compounds of formula (16) with *s*-BuLi at temperature ranging from  $-90\text{ }^\circ\text{C}$  to  $-60\text{ }^\circ\text{C}$  and then reaction with a boronic ester of formula (21) or an organotin compound of formula (22). Compounds of formula (23) can be reacted with compounds of formula (17) in the presence of a palladium catalyst, such as, but not limited to  $\text{Pd}(\text{OAc})_2$ ,  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{PdCl}_2(\text{dppf})$ ,  $\text{Pd}_2(\text{dba})_3$ , and a base, such as but not limited to CsF,  $\text{Na}_2\text{CO}_3$ ,  $\text{K}_2\text{CO}_3$  and  $\text{K}_3\text{PO}_4$  to provide compounds of formula (III).

Scheme 7



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The compounds of formula (III), wherein  $\text{Ar}^2$  and  $\text{Ar}^3$  are as previously defined can be prepared as shown in Scheme 7. Compounds of formula (24), where in  $\text{Ar}^2$  is defined in formulas (II) and (III), when treated with trimethyloxonium tetrafluoroborate in dichloromethane provide compounds of formula (25) as described by McClelland, R. A. in *J. Am. Chem. Soc.* (1978, 100, 1844-1849). Compounds of formula (25) can be reacted with compounds of formula (12), wherein  $\text{Ar}^3$  is defined in formulas (II) and (III), at temperature ranging from  $80\text{--}140\text{ }^\circ\text{C}$  over 1-6 hours to give compounds of formula (26). Compounds of formula (26) react with hydroxylamine in acetic acid at room temperature to  $90\text{ }^\circ\text{C}$  to provide the compounds of formula (III) as described by Lin, Y.-I., et al., *J. Org. Chem.*, 44, 4160-4164, 1979.

30

In addition, compounds of formula (II) and (III), wherein at least one of  $\text{Ar}^1$  and  $\text{Ar}^2$  is a N-containing heteroaryl, can be converted to compounds with  $\text{N}^+-\text{O}^-$  by treatment with an oxidizing agent. Examples of the oxidizing agent include, but are not limited to aqueous hydrogen peroxide and *m*-chloroperbenzoic acid. The reaction is generally performed in a

solvent such as, but not limited to acetonitrile, water, dichloromethane, acetone or a mixture thereof, preferably a mixture of acetonitrile and water, at a temperature from about 0° C to about 80 °C, for a period of about 1 hour to about 4 days.

The compounds and intermediates of the invention may be isolated and purified by methods well-known to those skilled in the art of organic synthesis. Examples of conventional methods for isolating and purifying compounds can include, but are not limited to, chromatography on solid supports such as silica gel, alumina, or silica derivatized with alkylsilane groups, by recrystallization at high or low temperature with an optional pretreatment with activated carbon, thin-layer chromatography, distillation at various pressures, sublimation under vacuum, and trituration, as described for instance in "Vogel's Textbook of Practical Organic Chemistry", 5th edition (1989), by Furniss et al., pub. Longman Scientific & Technical, Essex CM20 2JE, England.

Compounds and processes suitable for preparing compounds for the composition of the invention will be better understood in connection with the following Examples, which are intended as an illustration of and not a limitation upon the scope of the invention.

#### Preparation of 2,5-Disubstituted-1,3,4-Oxadiazole Derivatives

Suitable 2,5-disubstituted-1,3,4-oxadiazole derivatives were prepared using readily available starting materials. For example, International Publication WO 02/100826, published December 19, 2002, describes the preparation of some oxadiazole derivatives. However, Compounds of formula (I) also can be prepared according to the following general methods.

Method A: A carboxylic acid (0.5 mmol) and an acyl hydrazide (0.5 mmol) were combined in POCl<sub>3</sub> (2 mL) and stirred at 80-90 °C for 2-4 hours. The reaction mixture was then cooled down to ambient temperature and poured into ice water (10-20 g) and basified with saturated aqueous sodium carbonate to pH=8-9. The resultant precipitate was filtered, dried and purified with chromatography on silica gel to provide the corresponding 2,5-disubstituted-1,3,4-oxadiazole. The free base was then dissolved in EtOAc (5-10 mL) and treated with HCl (Aldrich, 4 M in dioxane, 2-3 eq.) at ambient temperature for 5-10 hours. The precipitate was filtered and dried to provide the corresponding 2,5-disubstituted-1,3,4-oxadiazole hydrochloric acid salt.

Method B: A Smith Process vial (0.5-2 ml) was charged with a stir bar. To the vessel were added a carboxylic acid (0.1 mmol), nicotinic hydrazide (Aldrich, 13.7 mg, 0.1 mmol),

PS-PPh<sub>3</sub> (Fluka, 2.2 mmol/g, 136 mg, 0.3 mmol) and Acetonitrile (anhydrous, Aldrich, 2 mL), followed by CCl<sub>3</sub>CN (Aldrich, 28.8 mg, 0.20 mmol). The reaction vessel was sealed and heated to 150 °C for 15 minutes using an Emrys™ Optimizer Microwave (Personal Chemistry, www.personalchemistry.com). After cooling, the reaction vessel was uncapped and the resin was removed by filtration. The mixture was purified by preparative HPLC [Waters, column: Nova-Pak® HR C18 6µm 60Å Prep-Pak® (25mm × 100mm), solvent: acetonitrile/water (v.1% TFA), 5/95 to 95/5, flow rate of 40 mL/minute. Fractions were collected based upon UV signal threshold, and selected fractions were subsequently analyzed by flow injection analysis mass spectrometry using positive APCI ionization on a Finnigan LCQ using 70:30 methanol:10 mM NH<sub>4</sub>OH(aq) at a flow rate of 0.8 mL/minute.]. Some mixtures were purified by an alternative preparative HPLC method [Waters, column: Sunfire OBD C8 5µm (30 mm x 75 mm); solvent: acetonitrile/10 mM aqueous ammonium acetate, 10/90 to 100/0; flow rate of 50 mL/minute]. Fractions were collected based upon target mass signal threshold, and selected fractions were subsequently analyzed by flow injection analysis mass spectrometry using the previously described method.

#### Preparation of 2,5-Disubstituted-1,2,4-Oxadiazole Derivatives

Suitable 2,5-disubstituted-1,2,4-oxadiazole derivatives were prepared using readily available starting materials. For example, International Publication WO 02/100826, published December 19, 2002, describes the preparation of some oxadiazole derivatives. However, compounds of formula (II) and (III) also can be prepared according to the following general methods.

Method C: To a solution of an aryl or heteroaryl carboxylic acid (1.0 mmol) in dimethylformamide (anhydrous, 5 mL) was added N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC) (Aldrich, 192 mg, 1.00 mmol) and 1-hydroxybenzotriazole (HOBt) hydrate (Fluka, 153 mg, 1.00 mmol). The mixture was stirred at ambient temperature for 20 minutes. N'-Hydroxy aryl or heteroaryl carboximidamide (1.0 mmol) was added and the mixture was stirred for 6–10 hours, and then warmed to 140 °C for 2-4 hours. The reaction was cooled to ambient temperature and triturated with water (10 mL). The precipitate was filtered and dried under vacuum to give the titled compound. When the reaction mixture failed to give a precipitate, the reaction mixture was extracted with EtOAc (3 x 30 mL). The combined extracts were concentrated and the residue was purified with chromatography (SiO<sub>2</sub>, hexane/EtOAc) or preparative HPLC [Waters, column:

Xbridge™ Prep C18 5 μm, OBD™ 30 x 100 mm, solvent: acetonitrile/water (pH=10, prepared with NH<sub>4</sub>HCO<sub>3</sub>/NH<sub>3</sub>·H<sub>2</sub>O) or acetonitrile/water(v/v 0.1% TFA), 5/95 to 95/5, flow rate of 40 mL/minute. Fractions were collected based upon UV signal threshold.].

Method D: To a solution of *N'*-Hydroxy aryl or heteroaryl carboximidamide (1.0 mmol) in pyridine (5 mL) was added an aryl or heteroaryl carbonyl chloride (1.0 mmol). The mixture was then stirred at the temperature ranging from 80–100 °C for 2–10 hours. The reaction was cooled to ambient temperature and triturated with water (10 mL). The precipitate was filtered and dried under vacuum to give the titled compound. When the reaction mixture failed to give a precipitate, the reaction mixture was extracted with EtOAc (3 x 30 mL). The combined extracts were concentrated and the residue was purified with chromatography (SiO<sub>2</sub>, hexane/EtOAc ) or preparative HPLC [Waters, column: Xbridge™ Prep C18 5μm, OBD™ 30 x 100 mm, solvent: acetonitrile/water (pH=10) or acetonitrile/water(v/v 0.1% TFA), 5/95 to 95/5, flow rate of 40 mL/minute. Fractions were collected based upon UV signal threshold.].

#### Example 1

##### 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile

3-Pyridylamideoxime (Aldrich, 5.5 g, 40 mmol) was dissolved in 60 mL of pyridine and 3-cyanobenzoyl chloride (Aldrich, 6.6 g, 40 mmol) was added. The reaction mixture was heated to reflux for 4 hours and then cooled to room temperature. The solution was poured into water (500 mL), filtered, and the solid were collected and dried under vacuum. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ ppm 7.87 (td, *J*=8.0, 0.7 Hz, 1 H), 8.10 (dt, *J*=8.1, 1.4 Hz, 1 H), 8.23 (ddd, *J*=8.1, 5.6, 0.8 Hz, 1 H), 8.56 (ddd, *J*=8.0, 1.7, 1.2 Hz, 1 H), 8.64 (td, *J*=1.7, 0.7 Hz, 1 H), 9.04 (dd, *J*=5.4, 1.0 Hz, 1 H), 9.23 (dt, *J*=8.1, 1.7 Hz, 1 H), 9.57 (d, *J*=1.7 Hz, 1 H); MS (+ESI) *m/z* 249 (M+H)<sup>+</sup>.

#### Example 2

##### 3,5-di(pyridin-3-yl)-1,2,4-oxadiazole

3-Pyridylamideoxime (5.5 g, 40 mmol) was dissolved in 60 mL of pyridine and nicotinoyl chloride hydrochloride (7.2 g, 40 mmol) was added. The reaction mixture was

heated to reflux for 4 hours and then cooled to room temperature. The solution was poured into water (500 mL), basified, filtered, and the solid was collected and dried under vacuum. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.75-7.65 (m, 2H), 8.49-8.45 (m, 1 H), 8.60-8.57 (m, 1 H), 8.84-8.82 (dd, *J*= 1.7 Hz, 1 H), 8.92-8.90 (dd, *J*= 1.7 Hz, 1 H), 9.28 (m, 1 H), 9.37 (m, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 225 (M+H)<sup>+</sup>.

### Example 3

#### 3-(5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzonitrile

### Example 3A

#### 3-Cyano-N<sup>1</sup>-hydroxybenzimidamide

Hydroxylamine (Aldrich, 7.65 g, 100 mmol) in ethanol (100 mL) was treated with 10 N sodium hydroxide (10 mL, 100 mmol). To this solution, isophthalonitrile (Aldrich, 12.8 g, 100 mmol) in 100 mL ethanol was added. The reaction mixture was heated to reflux for 3 hours and then cooled to room temperature. The solvent was removed under vacuum and the residue was purified with flash column chromatography (5% methanol/dichloromethane) to provide the titled compound. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 5.98 (bs, 2 H), 7.59 (t, *J*= 7.4 Hz, 1 H), 8.06-8.0 (m, 2 H), 9.89 (s, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 162 (M+H)<sup>+</sup>.

### Example 3B

#### 3-(5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzonitrile

3-Cyano-N<sup>1</sup>-hydroxybenzimidamide (0.322 g, 1 mmol) was dissolved in pyridine (10 mL) and nicotinoyl chloride (Aldrich, 0.141 g, 1 mmol) was added. The reaction mixture was heated to reflux for 3 hours and cooled to room temperature. The cooled reaction mixture was quenched with water (25 mL) and filtered. The solid was further purified with flash column chromatography (5% methanol/dichloromethane) to give the titled compound. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.75-7.71 (dd, *J*= 5.7, 4.1 Hz, 1 H), 7.85 (t, *J*= 7.8 Hz, 1 H), 8.15-8.12 (d, *J*= 7.8 Hz, 1 H) 8.44-8.42 (m, 1 H), 8.50 (m, 1 H), 8.60-8.56 (m, 1 H), 8.93-8.91 (dd, *J*= 1.7 Hz, 1 H), 9.37-9.38 (d, *J*= 1.7 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 249 (M+H)<sup>+</sup>.

### Example 4

#### 3-(5-(6-fluoropyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzonitrile

Example 4A3-Cyano-N'-hydroxybenzimidamide

Hydroxylamine (Aldrich, 7.65 g, 100 mmol) in ethanol (100 mL) was treated with 10  
5 N NaOH (10 mL, 100 mmol). To this solution, isophthalonitrile (Aldrich, 12.8 g, 100 mmol)  
in 100 mL of ethanol was added. The reaction mixture was heated to reflux for 3 hours and  
then cooled to room temperature. The solvent was removed under vacuum and the residue  
was purified with flash column chromatography (5% methanol/dichloromethane) to give the  
titled product. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 5.98 (bs, 2 H), 7.59 (t, *J*= 7.4 Hz, 1 H),  
10 8.06-8.0 (m, 2 H), 9.89 (s, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 162 (M+H)<sup>+</sup>.

Example 4B3-(5-(6-fluoropyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzonitrile

3-Cyano-N'-hydroxybenzimidamide (0.322 g, 1 mmol) was dissolved in pyridine 10  
mL and 6-fluoronicotinoyl chloride (Frontier Scientific, 0.160 g, 1 mmol) was added. The  
15 reaction mixture was heated to reflux for 3 hours and then cooled to room temperature. The  
cooled reaction mixture was quenched with water (25 mL) and filtered. The solid was further  
purified with flash column chromatography (5% methanol/dichloromethane) to give the titled  
product. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.56-7.52 (m, 1 H), 7.85 (t, *J*= 7.9 Hz, 1 H), 8.15-  
20 8.12 (m, 1 H), 8.43-8.41 (m, 1 H), 8.49 (m, 1 H), 8.8-8.74 (m, 1 H), 9.11-9.0 (m, 1 H) ppm;  
MS (DCI/NH<sub>3</sub>) *m/z* 267 (M+H)<sup>+</sup>.

Example 55-(5-bromopyridin-3-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

25 The title compound was prepared according to the procedure of Example 1 using *N'*-  
hydroxynicotinimidamide (Aldrich) and 5-bromonicotinoyl chloride (Alfa). <sup>1</sup>H NMR (300  
MHz, DMSO-*d*<sub>6</sub>) δ 8.65-8.69 (m, 1 H), 8.45-8.49 (m, 1 H), 8.79 (t, *J*= 1.7 Hz, 1 H), 8.84 (dd,  
*J*=1.7, 2.0 Hz, 1 H), 9.07 (d, *J*= 2 Hz, 1 H), 9.28-9.29 (m, 1 H), 9.34 (d, *J*= 1.7 Hz, 1 H) ppm;  
MS (DCI/NH<sub>3</sub>) *m/z* 303 (M+H)<sup>+</sup>.

30

Example 63-(pyridin-3-yl)-5-(3-(trifluoromethylsulfonyl)phenyl)-1,2,4-oxadiazole

Example 6A3-(trifluoromethylsulfonyl)benzoic acid

A solution of 3-(trifluoromethylthio)benzoic acid (222 mg, 1 mmol) in dichloromethane (10 mL) was stirred with chromium(VI) oxide (Aldrich, 2.0 mmol) at ambient temperature for 12 hours. The title compound was obtained by directly loading the reaction mixture onto a silica gel column and eluting with dichloromethane/methanol (9:1).  
<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 8.8 (s, 1 H), 8.28 (m, 1 H), 8.05 (m, 1 H), 7.9(m, 1 H) ppm; MS (DCI/NH<sub>3</sub>) m/z 255 (M+H)<sup>+</sup>.

Example 6B3-(trifluoromethylsulfonyl)benzoyl chloride

A solution of the product of Example 6A (198 mg, 0.8 mmol) in dichloromethane (10 mL) was stirred with oxalyl dichloride (Aldrich, 2.0 mmol) and 1 drop of dimethylformamide at ambient temperature for 2 hours. The title compound was obtained by removing the solvent under vacuum as a yellow oil (250 mg) and the compound was used directly in the next step.

Example 6C3-(pyridin-3-yl)-5-(3-(trifluoromethylsulfonyl)phenyl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 1 using *N*'-hydroxynicotinimidamide (Aldrich) and the compound of Example 6B. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.73 (dd, *J*=4, 5.0 Hz, 1 H), 7.85 (t, *J*= 8 Hz, 1 H), 8.13 (m, 1 H), 8.43 (m, 1 H) 8.5 (m, 1 H), 8.6 (m, 1 H), 8.92 (m, 1 H), 9.37 (m, 1 H) ppm; MS (DCI/NH<sub>3</sub>) m/z 356 (M+H)<sup>+</sup>.

Example 73-(3-(6-methylpyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrileExample 7A*N*'-hydroxy-6-methylnicotinimidamide

Hydroxylamine (Aldrich, 0.765 g, 10 mmol) in ethanol (10 mL) was treated with a solution 6-methylnicotinonitrile (Aldrich, 12.8 g, 100 mmol) in ethanol (10 mL). The reaction mixture was heated to reflux for 3 hours and then cooled to room temperature. The

solvent was removed under vacuum and the residue was purified with flash column chromatography (5% methanol/dichloromethane) give the titled compound.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-}d_6$ )  $\delta$  2.2 (s, 3 H), 6.02 (bs, 2 H), 7.59 (m, 1 H), 8.06-8.0 (m, 2 H), 10.2 (s, 1 H) ppm; MS (DCI/ $\text{NH}_3$ )  $m/z$  152 ( $\text{M}+\text{H}$ ) $^+$ .

5

#### Example 7B

##### 3-(3-(6-methylpyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzonitrile

The titled compound was prepared according to the procedure of Example 1 using *N'*-hydroxynicotinimidamide (Example 7A) and 3-cyanobenzoyl chloride (Aldrich).  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-}d_6$ )  $\delta$  2.59 (s, 3H), 7.52 (d,  $J=8.1$  Hz, 1 H), 7.39 (t,  $J=8.5$  Hz, 1 H), 8.23-8.21 (m, 1 H), 8.36-8.32 (m, 1 H), 8.53-8.49 (m, 1 H), 8.64 (m, 1 H), 9.14 (m, 1 H), ppm; MS (DCI/ $\text{NH}_3$ )  $m/z$  263 ( $\text{M}+\text{H}$ ) $^+$ .

10

#### Example 8

##### 5-(5-(pyrrol-1-yl)pyridin-3-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

To a solution of 5-(1H-pyrrol-1-yl)nicotinic acid (Maybridge, 188 mg, 1.00 mmol) in dimethylformamide (anhydrous, 5 mL) was added N-(3-methylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC) (Aldrich, 192 mg, 1.00 mmol) and 1-hydroxybenzotriazole (HOBT) hydrate (Fluka, 153 mg, 1.00 mmol). The mixture was stirred at ambient temperature for 20 minutes. *N'*-Hydroxynicotinimidamide (137 mg, 1.0 mmol) was added and the mixture was stirred for 6–10 hours, and then warmed to 140 °C for 2-4 hours. The reaction was cooled to ambient temperature and triturated with water (10 mL). The precipitate was filtered and dried under vacuum to give the titled compound.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-}d_6$ )  $\delta$  6.34 - 6.44 (m, 2 H), 7.60 - 7.82 (m, 3 H), 8.50 (dt,  $J=8.1, 1.9$  Hz, 1 H), 8.71 (dd,  $J=2.5, 1.9$  Hz, 1 H), 8.84 (dd,  $J=4.6, 1.5$  Hz, 1 H), 9.21 (d,  $J=1.7$  Hz, 1 H), 9.26 (d,  $J=2.4$  Hz, 1 H), 9.31 (d,  $J=1.7$  Hz, 1 H) ppm; MS (DCI/ $\text{NH}_3$ )  $m/z$  290 ( $\text{M}+\text{H}$ ) $^+$ .

20

25

#### Example 9

##### 5-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)pyridin-3-ol

The title compound was prepared according to the procedure of Example 8 using *N'*-hydroxynicotinimidamide (Aldrich) and 5-hydroxynicotinic acid (Matrix Scientific).  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-}d_6$ )  $\delta$  7.66 (ddd,  $J=8.0, 4.9, 1.0$  Hz, 1 H), 7.86 (dd,  $J=2.7, 2.0$  Hz, 1 H), 8.31 - 8.55 (m, 2 H), 8.83 (s, 2 H), 9.26 (s, 1 H) ppm; MS (DCI/ $\text{NH}_3$ )  $m/z$  241 ( $\text{M}+\text{H}$ ) $^+$ .

30

Example 105-(3,4-difluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

5 The title compound was prepared according to the procedure of Example 8 using *N*'-hydroxynicotinimidamide (Aldrich) and 3,4-difluorobenzoic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.52 - 7.67 (m, 2 H), 8.12 (ddd, *J*=8.7, 4.3, 1.5 Hz, 1 H), 8.19 (ddd, *J*=10.8, 7.5, 2.0 Hz, 1 H), 8.55 (dt, *J*=8.1, 1.9 Hz, 1 H), 8.74 (dd, *J*=5.1, 1.7 Hz, 1 H), 9.29 (dd, *J*=2.0, 0.7 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 260 (M+H)<sup>+</sup>.

10

Example 115-(2,3-difluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 8 using *N*'-hydroxynicotinimidamide (Aldrich) and 2,3-difluorobenzoic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.51 - 7.67 (m, 2 H), 8.08 - 8.14 (m, 1 H), 8.18 (ddd, *J*=10.7, 7.5, 2.0 Hz, 1 H), 8.55 (dt, *J*=8.0, 1.9 Hz, 1 H), 8.74 (dd, *J*=5.2, 1.6 Hz, 1 H), 9.29 (dd, *J*=2.4, 0.8 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 260 (M+H)<sup>+</sup>.

15

Example 125-(pyrazin-2-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

20 The titled compound was prepared according to the procedure of Example 8 using *N*'-hydroxynicotinimidamide (Aldrich) and pyrazine-2-carboxylic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.66 (ddd, *J*=8.0, 4.9, 1.0 Hz, 1 H), 8.60 (dt, *J*=8.0, 1.9 Hz, 1 H), 8.77 (dd, *J*=5.0, 1.8 Hz, 1 H), 8.86 - 8.89 (m, 1 H), 8.89 - 8.91 (m, 1 H), 9.34 (dd, *J*=2.4, 0.8 Hz, 1 H), 9.56 (d, *J*=1.6 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 226 (M+H)<sup>+</sup>.

25

Example 135-(3,5-difluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

30 The title compound was prepared according to the procedure of Example 8 using *N*'-hydroxynicotinimidamide (Aldrich) and 3,5-difluorobenzoic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.37 (tt, *J*=9.0, 2.3 Hz, 1 H), 7.65 (ddd, *J*=7.9, 5.0, 1.0 Hz, 1 H), 7.82 - 7.91 (m, 2 H), 8.56 (dt, *J*=7.9, 2.0 Hz, 1 H), 8.75 (dd, *J*=4.8, 1.6 Hz, 1 H), 9.30 (dd, *J*=2.0, 0.8 Hz,

1 H)ppm; MS (DCI/NH<sub>3</sub>) m/z 260 (M+H)<sup>+</sup>.

#### Example 14

##### 5-(2,3,5-trifluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

5 The title compound was prepared according to the procedure of Example 8 using *N*'-hydroxynicotinimidamide (Aldrich) and 2,3,5-trifluorobenzoic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.55 - 7.68 (m, 2 H), 7.83 - 7.90 (m, 1 H), 8.57 (dt, *J*=8.1, 1.9 Hz, 1 H), 8.75 (dd, *J*=5.1, 1.7 Hz, 1 H), 9.30 (dd, *J*=2.2, 0.8 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) m/z 278 (M+H)<sup>+</sup>.

#### Example 15

##### 5-(2,4,5-trifluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

10 The title compound was prepared according to the procedure of Example 8 using *N*'-hydroxynicotinimidamide (Aldrich) and 2,4,5-trifluorobenzoic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.55 (td, *J*=10.3, 6.4 Hz, 1 H), 7.64 (ddd, *J*=8.1, 5.0, 0.8 Hz, 1 H), 8.23 (ddd, *J*=10.3, 8.6, 6.4 Hz, 1 H), 8.56 (dt, *J*=8.1, 1.9 Hz, 1 H), 8.75 (dd, *J*=5.1, 1.7 Hz, 1 H), 9.29 (d, *J*=1.4 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) m/z 278 (M+H)<sup>+</sup>.

#### Example 16

##### 5-(2,5-difluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

20 The title compound was prepared according to the procedure of Example 8 using *N*'-hydroxynicotinimidamide (Aldrich) and 2,5-difluorobenzoic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.41 - 7.56 (m, 2 H), 7.65 (ddd, *J*=7.9, 5.0, 1.0 Hz, 1 H), 7.98 - 8.04 (m, 1 H), 8.57 (dt, *J*=8.0, 1.9 Hz, 1 H), 8.75 (dd, *J*=5.2, 1.6 Hz, 1 H), 9.31 (dd, *J*=2.0, 0.8 Hz, 1 H); MS (DCI/NH<sub>3</sub>) m/z 260 (M+H)<sup>+</sup>.

#### Example 17

##### 5-(4-chloro-2,5-difluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

25 The title compound was prepared according to the procedure of Example 8 using *N*'-hydroxynicotinimidamide (Aldrich) and 4-chloro-2,5-difluorobenzoic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.65 (ddd, *J*=8.0, 4.9, 1.0 Hz, 1 H), 7.73 (dd, *J*=9.7, 5.9 Hz, 1

H), 8.18 (dd,  $J=8.8, 6.1$  Hz, 1 H), 8.57 (dt,  $J=8.1, 1.9$  Hz, 1 H), 8.75 (dd,  $J=4.7, 1.7$  Hz, 1 H), 9.30 (dd,  $J=2.2, 0.8$  Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  294 (M+H)<sup>+</sup>.

#### Example 18

##### 5-(5-methylpyrazin-2-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 8 using N'-hydroxynicotinimidamide (Aldrich) and 5-methylpyrazine-2-carboxylic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  2.71 (s, 3 H), 7.66 (ddd,  $J=8.0, 5.1, 0.8$  Hz, 1 H), 8.59 (dt,  $J=7.9, 1.8$  Hz, 1 H), 8.74 - 8.78 (m, 2 H), 9.33 (dd,  $J=2.0, 0.8$  Hz, 1 H), 9.40 (d,  $J=1.2$  Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  240 (M+H)<sup>+</sup>.

#### Example 19

##### 4-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile

The title compound was prepared according to the procedure of Example 1 using N'-hydroxynicotinimidamide (Aldrich) and 4-cyanobenzoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  7.65 (ddd,  $J=8.0, 4.9, 1.0$  Hz, 1 H), 8.02 (d,  $J=8.8$  Hz, 2 H), 8.42 (d,  $J=8.8$  Hz, 2 H), 8.57 (dt,  $J=8.1, 1.9$  Hz, 1 H), 8.75 (dd,  $J=4.7, 1.7$  Hz, 1 H), 9.31 (dd,  $J=2.2, 0.8$  Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  249 (M+H)<sup>+</sup>.

#### Example 20

##### 2,3,6-trifluoro-5-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenol

The title compound was prepared according to the procedure of Example 8 using N'-hydroxynicotinimidamide (Aldrich) and 2,4,5-trifluoro-3-hydroxybenzoic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  7.63 - 7.76 (m, 2 H), 8.44 (dt,  $J=7.9, 2.0$  Hz, 1 H), 8.83 (dd,  $J=4.8, 1.6$  Hz, 1 H), 9.25 (d,  $J=1.6$  Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  294 (M+H)<sup>+</sup>.

#### Example 21

##### 2-fluoro-5-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenol

The title compound was prepared according to the procedure of Example 8 using N'-hydroxynicotinimidamide (Aldrich) and 4-fluoro-3-hydroxybenzoic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.45 (dd,  $J=11.1, 8.7$  Hz, 1 H), 7.62 - 7.71 (m, 2 H), 7.78 (dd,  $J=8.3,$

2.0 Hz, 1 H), 8.43 (dt,  $J=7.9$ , 1.8 Hz, 1 H), 8.82 (dd,  $J=5.0$ , 1.8 Hz, 1 H), 9.24 (d,  $J=2.0$  Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  258 (M+H)<sup>+</sup>.

#### Example 22

##### 5 2-fluoro-4-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenol

The title compound was prepared according to the procedure of Example 8 using *N'*-hydroxynicotinimidamide (Aldrich) and 3-fluoro-4-hydroxybenzoic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  7.09 (t,  $J=8.7$  Hz, 1 H), 7.63 (ddd,  $J=7.9$ , 5.2, 0.8 Hz, 1 H), 7.86 - 7.93 (m, 2 H), 8.53 (dt,  $J=7.9$ , 2.0 Hz, 1 H), 8.72 (dd,  $J=4.8$ , 1.6 Hz, 1 H), 9.27 (dd,  $J=2.4$ , 0.8 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  258 (M+H)<sup>+</sup>.

#### Example 23

##### 15 5-(3-chloro-4-fluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 8 using *N'*-hydroxynicotinimidamide (Aldrich) and 3-chloro-4-fluorobenzoic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  7.54 (t,  $J=8.8$  Hz, 1 H), 7.64 (ddd,  $J=8.1$ , 5.0, 0.8 Hz, 1 H), 8.24 (ddd,  $J=8.6$ , 4.6, 2.0 Hz, 1 H), 8.39 (dd,  $J=7.0$ , 2.2 Hz, 1 H), 8.55 (dt,  $J=8.1$ , 1.9 Hz, 1 H), 8.74 (dd,  $J=4.9$ , 1.5 Hz, 1 H), 9.29 (dd,  $J=2.2$ , 0.8 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  276 (M+H)<sup>+</sup>.

#### Example 24

##### 20 5-(3,4-dichlorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 8 using *N'*-hydroxynicotinimidamide (Aldrich) and 3,4-dichlorobenzoic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  7.64 (ddd,  $J=8.0$ , 5.1, 0.8 Hz, 1 H), 7.82 (d,  $J=8.3$  Hz, 1 H), 8.14 - 8.19 (m, 1 H), 8.40 (d,  $J=2.0$  Hz, 1 H), 8.56 (dt,  $J=7.9$ , 2.0 Hz, 1 H), 8.75 (dd,  $J=5.2$ , 1.6 Hz, 1 H), 9.29 (dd,  $J=2.2$ , 1.0 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  292 (M+H)<sup>+</sup>.

#### Example 25

##### 30 2-nitro-5-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenol

The title compound was prepared according to the procedure of Example 8 using *N'*-hydroxynicotinimidamide (Aldrich) and 3-hydroxy-4-nitrobenzoic acid (Maybridge). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  6.51 (d,  $J=9.1$  Hz, 1 H), 6.92 - 7.31 (s (broad), 1 H), 7.61 (ddd,  $J=7.9$ , 4.8, 0.8 Hz, 1 H), 7.68 (dd,  $J=9.1$ , 2.4 Hz, 1 H), 8.40 (dt,  $J=7.9$ , 2.0 Hz, 1 H),

8.53 (d,  $J=2.4$  Hz, 1 H), 8.77 (dd,  $J=4.8, 1.6$  Hz, 1 H), 9.20 (d,  $J=1.6$  Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  285 (M+H)<sup>+</sup>.

#### Example 26

5                    5-(2,3,6-trifluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 8 using *N'*-hydroxynicotinimidamide (Aldrich) and 2,3,6-trifluorobenzoic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  7.26 - 7.35 (m,  $J=9.4, 9.4, 3.8, 2.0$  Hz, 1 H), 7.62 - 7.77 (m, 2 H), 8.57 (dt,  $J=8.0, 1.9$  Hz, 1 H), 8.76 (dd,  $J=4.8, 1.6$  Hz, 1 H), 9.30 (dd,  $J=2.4, 0.8$  Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  278 (M+H)<sup>+</sup>.

#### Example 27

15                    2,2,2-trifluoro-1-(4-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenyl)ethanone trifluoroacetate

The title compound was prepared according to the procedure of Example 8 using *N'*-hydroxynicotinimidamide (Aldrich) and 4-(2,2,2-trifluoroacetyl)benzoic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  7.81 (ddd,  $J=7.9, 5.2, 0.8$  Hz, 1 H), 7.96 (d,  $J=8.3$  Hz, 2 H), 8.28 (d,  $J=8.7$  Hz, 2 H), 8.76 (dt,  $J=8.2, 1.8$  Hz, 1 H), 8.82 (dd,  $J=5.2, 1.6$  Hz, 1 H), 9.38 (d,  $J=1.6$  Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  320 (M+H)<sup>+</sup>.

#### Example 28

20                    5-(3-fluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 8 using *N'*-hydroxynicotinimidamide (Aldrich) and 3-fluorobenzoic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  7.43 - 7.51 (m,  $J=8.5, 8.5, 2.6, 1.0$  Hz, 1 H), 7.61 - 7.72 (m, 2 H), 7.98 (ddd,  $J=9.1, 2.6, 1.4$  Hz, 1 H), 8.08 (ddd,  $J=8.0, 1.3, 1.0$  Hz, 1 H), 8.56 (dt,  $J=8.0, 1.9$  Hz, 1 H), 8.74 (dd,  $J=5.2, 1.6$  Hz, 1 H), 9.30 (dd,  $J=2.0, 0.8$  Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  242 (M+H)<sup>+</sup>.

#### Example 29

30                    5-(4-fluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 8 using *N'*-hydroxynicotinimidamide (Aldrich) and 4-fluorobenzoic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  7.39 (t,  $J=8.9$  Hz, 2 H), 7.64 (ddd,  $J=7.9, 4.8, 0.8$  Hz, 1 H), 8.27 - 8.35 (m, 2 H), 8.55 (ddd,  $J=8.1, 2.0, 1.8$  Hz, 1 H), 8.74 (dd,  $J=5.0, 1.8$  Hz, 1 H), 9.29 (dd,  $J=2.2, 1.0$  Hz, 1

H) ppm; MS (DCI/NH<sub>3</sub>) m/z 242 (M+H)<sup>+</sup>.

Example 30

5-(2-fluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 8 using N'-  
5 hydroxynicotinimidamide (Aldrich) and 2-fluorobenzoic acid (Aldrich). <sup>1</sup>H NMR (300 MHz,  
CD<sub>3</sub>OD) δ 7.38 - 7.49 (m, 2 H), 7.64 (ddd, *J*=8.0, 4.9, 1.0 Hz, 1 H), 7.70 - 7.79 (m, 1 H), 8.28  
(td, *J*=7.5, 1.9 Hz, 1 H), 8.57 (dt, *J*=8.1, 1.9 Hz, 1 H), 8.74 (dd, *J*=4.7, 1.7 Hz, 1 H), 9.31 (dd,  
*J*=2.2, 0.8 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) m/z 242 (M+H)<sup>+</sup>.

Example 31

3-fluoro-5-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile

The title compound was prepared according to the procedure of Example 8 using N'-  
10 hydroxynicotinimidamide (Aldrich) and 3-cyano-5-fluorobenzoic acid (Aldrich). <sup>1</sup>H NMR  
(300 MHz, CD<sub>3</sub>OD) δ 7.65 (ddd, *J*=8.0, 5.1, 0.8 Hz, 1 H), 7.95 (ddd, *J*=8.1, 2.6, 1.6 Hz, 1 H),  
8.32 (ddd, *J*=8.7, 2.6, 1.4 Hz, 1 H), 8.46 (t, *J*=1.4 Hz, 1 H), 8.58 (ddd, *J*=8.1, 2.0, 1.8 Hz, 1  
15 H), 8.76 (dd, *J*=5.2, 1.6 Hz, 1 H), 9.31 (dd, *J*=2.0, 0.8 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) m/z 267  
(M+H)<sup>+</sup>.

Example 32

3-(2,3-difluorophenyl)-5-(pyridin-3-yl)-1,2,4-oxadiazole hydrochloric acid

20

Example 32A

3-(2,3-difluorophenyl)-5-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 1 using 2,3-  
difluoro-N'-hydroxybenzimidamide (Tyger Scientific) and nicotinoyl chloride hydrochloride  
25 (Aldrich). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.42 - 7.61 (m, 1 H), 7.67 - 7.85 (m, 2 H), 7.91  
- 8.04 (m, 1 H), 8.57 (dt, *J*=8.1, 1.9 Hz, 1 H), 8.92 (dd, *J*=4.8, 1.6 Hz, 1 H), 9.36 (dd, *J*=2.4,  
0.8 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) m/z 260 (M+H)<sup>+</sup>.

Example 32B

30

3-(2,3-difluorophenyl)-5-(pyridin-3-yl)-1,2,4-oxadiazole hydrochloric acid

A solution of the product of Example 32A (320 mg, 1.23 mmol) in ethyl acetate (5  
mL) was stirred with hydrochloric acid (Aldrich, 4 M in dioxane, 0.5 mL, 2.0 mmol) at

ambient temperature for 4 hours. The titled compound was collected by filtration and dried under vacuum.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.35 - 7.46 (m, 1 H), 7.49 - 7.63 (m, 1 H), 7.93 - 8.07 (m, 1 H), 8.24 (dd,  $J=8.1, 5.8$  Hz, 1 H), 9.10 (dd,  $J=5.8, 1.4$  Hz, 1 H), 9.23 (dt,  $J=8.0, 1.8$  Hz, 1 H), 9.66 (d,  $J=2.0$  Hz, 1 H) ppm; MS (DCI/ $\text{NH}_3$ )  $m/z$  260 ( $\text{M}+\text{H}$ ) $^+$ .

5

#### Example 33

#### 3-(3,4-difluorophenyl)-5-(pyridin-3-yl)-1,2,4-oxadiazole hydrochloric acid

#### Example 33A

#### 3-(3,4-difluorophenyl)-5-(pyridin-3-yl)-1,2,4-oxadiazole

10

The title compound was prepared according to the procedure of Example 1 using 3,4-difluoro- $N'$ -hydroxybenzimidamide (Tyger Scientific) and nicotinoyl chloride hydrochloride (Aldrich).  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$  7.74 (dd,  $J=7.5, 4.4$  Hz, 1 H), 8.60 (dt,  $J=7.8, 2.1$  Hz, 1 H), 8.93 (dd,  $J=4.8, 1.6$  Hz, 1 H), 9.38 (dd,  $J=2.2, 1.0$  Hz, 1 H), 9.44 - 9.48 (m, 3 H) ppm; MS (DCI/ $\text{NH}_3$ )  $m/z$  260 ( $\text{M}+\text{H}$ ) $^+$ .

15

#### Example 33B

#### 3-(3,4-difluorophenyl)-5-(pyridin-3-yl)-1,2,4-oxadiazole hydrochloric acid

A solution of the product of Example 32A (280 mg, 1.08 mmol) in ethyl acetate (5 mL) was stirred with hydrochloric acid (Aldrich, 4 M in dioxane, 0.5 mL, 2.0 mmol) at ambient temperature for 4 hours. The title compound was collected by filtration and dried under vacuum.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.52 (td,  $J=10.5, 8.3$  Hz, 1 H), 8.00 - 8.17 (m, 2 H), 8.26 (ddd,  $J=8.1, 5.8, 0.7$  Hz, 1 H), 9.08 - 9.14 (m, 1 H), 9.22 - 9.30 (m, 1 H), 9.66 (d,  $J=2.0$  Hz, 1 H) ppm; MS (DCI/ $\text{NH}_3$ )  $m/z$  260 ( $\text{M}+\text{H}$ ) $^+$ .

25

#### Example 34

#### 5-(2,6-difluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 8 using  $N'$ -hydroxynicotinimidamide (Aldrich) and 2,6-difluorobenzoic acid (Aldrich).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.29 (t,  $J=8.6$  Hz, 2 H), 7.65 (ddd,  $J=8.0, 4.9, 1.0$  Hz, 1 H), 7.77 (tt,  $J=8.6, 6.1$  Hz, 1 H), 8.57 (ddd,  $J=8.3, 1.9, 1.7$  Hz, 1 H), 8.75 (dd,  $J=4.7, 1.7$  Hz, 1 H), 9.30 (dd,  $J=2.2, 0.8$  Hz, 1 H) ppm; MS (DCI/ $\text{NH}_3$ )  $m/z$  260 ( $\text{M}+\text{H}$ ) $^+$ .

30

Example 353-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzenesulfonamide

The title compound was prepared according to the procedure of Example 8 using *N'*-hydroxynicotinimidamide (Aldrich) and 3-sulfamoylbenzoic acid (Oakwood). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.65 (ddd, *J*=8.0, 4.9, 1.0 Hz, 1 H), 7.83 (t, *J*=7.9 Hz, 1 H), 8.21 (ddd, *J*=7.9, 1.8, 1.0 Hz, 1 H), 8.45 (dt, *J*=7.9, 1.4 Hz, 1 H), 8.58 (dt, *J*=8.0, 1.9 Hz, 1 H), 8.73 - 8.77 (m, 2 H), 9.31 (dd, *J*=2.2, 1.0 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 303 (M+H)<sup>+</sup>.

Example 365-(2,4-difluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 8 using *N'*-hydroxynicotinimidamide (Aldrich) and 2,4-difluorobenzoic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.23 - 7.36 (m, 2 H), 7.64 (ddd, *J*=8.1, 5.0, 0.8 Hz, 1 H), 8.35 (td, *J*=8.5, 6.4 Hz, 1 H), 8.56 (dt, *J*=7.8, 1.9 Hz, 1 H), 8.74 (dd, *J*=5.1, 1.7 Hz, 1 H), 9.30 (dd, *J*=2.2, 0.8 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 260 (M+H)<sup>+</sup>.

Example 375-(2,3,4-trifluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 8 using *N'*-hydroxynicotinimidamide (Aldrich) and 2,3,4-trifluorobenzoic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.37 - 7.48 (m, *J*=9.3, 9.3, 7.1, 2.4 Hz, 1 H), 7.64 (ddd, *J*=7.9, 5.0, 1.0 Hz, 1 H), 8.08 - 8.18 (m, 1 H), 8.56 (dt, *J*=8.0, 1.9 Hz, 1 H), 8.75 (dd, *J*=5.0, 1.8 Hz, 1 H), 9.30 (dd, *J*=2.0, 0.8 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 278 (M+H)<sup>+</sup>.

Example 385-(3,4,5-trifluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 8 using *N'*-hydroxynicotinimidamide (Aldrich) and 3,4,5-trifluorobenzoic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.64 (ddd, *J*=8.0, 4.9, 1.0 Hz, 1 H), 8.01 - 8.13 (m, 2 H), 8.56 (ddd, *J*=8.1, 1.8, 1.6 Hz, 1 H), 8.75 (dd, *J*=4.8, 1.6 Hz, 1 H), 9.29 (dd, *J*=2.0, 0.8 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 278 (M+H)<sup>+</sup>.

Example 395-(4-chloro-3-fluorophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 8 using N'-hydroxynicotinimidamide (Aldrich) and 4-chloro-3-fluorobenzoic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.64 (ddd, *J*=7.9, 5.0, 1.0 Hz, 1 H), 7.78 (dd, *J*=8.3, 7.5 Hz, 1 H), 8.07 (ddd, *J*=8.3, 2.0, 0.8 Hz, 1 H), 8.12 (dd, *J*=9.5, 2.0 Hz, 1 H), 8.55 (dt, *J*=7.9, 2.0 Hz, 1 H), 8.74 (dd, *J*=5.0, 1.8 Hz, 1 H), 9.28 - 9.30 (m, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 276 (M+H)<sup>+</sup>.

Example 405-(3-nitrophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 8 using N'-hydroxynicotinimidamide (Aldrich) and 3-nitrobenzoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.44 - 7.55 (m, 1 H), 7.82 (t, *J*=8.3 Hz, 1 H), 8.43 - 8.60 (m, 3 H), 8.80 (dd, *J*=4.7, 1.7 Hz, 1 H), 9.07 - 9.13 (m, 1 H), 9.42 (d, *J*=2.0 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 269 (M+H)<sup>+</sup>.

Example 415-(3-(methylsulfonyl)phenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 8 using N'-hydroxynicotinimidamide (Aldrich) and 3-(methylsulfonyl)benzoic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 3.24 (s, 3 H), 7.65 (ddd, *J*=8.0, 4.9, 1.0 Hz, 1 H), 7.89 - 7.96 (m, 1 H), 8.28 (ddd, *J*=8.0, 1.9, 1.0 Hz, 1 H), 8.55 - 8.61 (m, 2 H), 8.75 (dd, *J*=5.1, 1.7 Hz, 1 H), 8.78 (t, *J*=1.5 Hz, 1 H), 9.32 (dd, *J*=2.2, 0.8 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 302 (M+H)<sup>+</sup>.

Example 423-(2-chloropyridin-4-yl)-5-(pyridin-3-yl)-1,2,4-oxadiazoleExample 42A2-chloro-N'-hydroxyisonicotinimidamide

A solution of 2-chloroisonicotinonitrile (Aldrich, 0.73 g, 5.27 mmol), and hydroxylamine (Aldrich, 50 wt%, 0.348 g, 5.27 mmol) in methanol (10 mL) was heated to reflux and stirred for 1 hour. The volatiles were removed under reduced pressure to give the title compound. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 6.09 (s, 2 H), 7.67 (dd, *J*=5.4, 1.4 Hz, 1

H), 7.73 (d,  $J=2.0$  Hz, 1 H), 8.40 (d,  $J=5.2$  Hz, 1 H), 10.22 (s, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  172 (M+H)<sup>+</sup>, 174 (M+H)<sup>+</sup>.

#### Example 42B

##### 5                    3-(2-chloropyridin-4-yl)-5-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 1 using the product of Example 42A and nicotinoyl chloride hydrochloride (Aldrich). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.73 (ddd,  $J=8.0, 4.9, 1.0$  Hz, 1 H), 8.04 - 8.13 (m, 2 H), 8.59 (dt,  $J=7.9, 2.0$  Hz, 1 H), 8.71 (d,  $J=5.2$  Hz, 1 H), 8.92 (dd,  $J=5.0, 1.8$  Hz, 1 H), 9.38 (dd,  $J=2.2, 1.0$  Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  259 (M+H)<sup>+</sup>, 261 (M+H)<sup>+</sup>.

#### Example 43

##### 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzamide

A solution of the product of Example 1 (248 mg, 1 mmol) in THF (10 ml) was stirred with potassium trimethylsilanolate (257 mg, 2.000 mmol) at 65 °C for 10 hours. It was then quenched with water (20 mL) and stirred at ambient temperature for 2 hours. The precipitate was filtered and dried under vacuum to give the title compound. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.67 (ddd,  $J=7.9, 4.8, 0.8$  Hz, 1 H), 7.78 (t,  $J=7.7$  Hz, 1 H), 8.23 (dt,  $J=8.1, 1.4, 1.2$  Hz, 1 H), 8.30 [s (broad, 2 H)], 8.36 (dt,  $J=8.1, 1.3$  Hz, 1 H), 8.48 (dt,  $J=7.9, 2.0$  Hz, 1 H), 8.68 - 8.73 (m, 1 H), 8.83 (dd,  $J=4.8, 1.6$  Hz, 1 H), 9.28 (dd,  $J=2.2, 1.0$  Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  267 (M+H)<sup>+</sup>.

#### Example 44

##### 25                    4-(5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one hydrochloric acid

A solution of the product of Example 42 (100 mg, 0.39 mmol) in concentrated hydrochloric acid (Aldrich, 36.5%, 3.0 mL) was heated in an Emry™ Creator microwave to 150 °C at 300 watts for 60 minutes. It was then concentrated. The residue was stirred in ethanol/ethyl acetate (v. 1/1, 5 mL) at ambient temperature for 1 hour. The title compound was collected by filtration and dried. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  6.75 (dd,  $J=6.7, 1.6$  Hz, 1 H), 7.04 (d,  $J=1.6$  Hz, 1 H), 7.61 (d,  $J=5.9$  Hz, 1 H), 7.67 - 7.81 (m, 1 H), 8.56 (dt,  $J=8.0, 1.9$  Hz, 1 H), 8.91 (dd,  $J=5.0, 1.8$  Hz, 1 H), 9.31 - 9.40 (m, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  241 (M+H)<sup>+</sup>.

Example 45

tert-butyl 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzoate

N'-Hydroxynicotinimidamide (274 mg, 2.00 mmol) was coupled with 3-(*tert*-  
5 butoxycarbonyl)benzoic acid (Aldrich) according to the procedure described in Example 8.  
<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 1.65 (s, 9 H), 7.65 (ddd, *J*=7.9, 4.8, 0.8 Hz, 1 H), 7.71 - 7.77  
(m, 1 H), 8.26 (ddd, *J*=7.7, 1.8, 1.6 Hz, 1 H), 8.42 - 8.46 (m, 1 H), 8.57 (dt, *J*=7.9, 2.0 Hz, 1  
H), 8.73 - 8.78 (m, 2 H), 9.31 (dd, *J*=2.2, 1.0 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 324 (M+H)<sup>+</sup>.

Example 46

2-amino-5-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenol

A solution of the product of Example 25 (284 mg, 1 mmol) in tetrahydrofuran (10  
mL) was stirred with Raney®-nickel (Aldrich, 100 mg) under hydrogen at ambient  
temperature for 2 hours. The catalyst was then removed by filtration and the organic solution  
15 concentrated to give the title compound. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 5.67 (s, 2 H),  
6.74 (d, *J*=8.1 Hz, 1 H), 7.41 - 7.50 (m, 2 H), 7.62 (dd, *J*=8.3, 4.6 Hz, 1 H), 8.39 (dt, *J*=8.2,  
1.9, 1.7 Hz, 1 H), 8.78 (dd, *J*=4.7, 1.7 Hz, 1 H), 9.20 (d, *J*=1.7 Hz, 1 H), 9.74 (s (broad), 1 H)  
ppm; MS (DCI/NH<sub>3</sub>) *m/z* 255 (M+H)<sup>+</sup>.

Example 47

*N,N*-dimethyl-4-(5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)pyridin-2-amine

A solution of the product of Example 42 (100 mg, 0.39 mmol) in dimethylformamide  
(2.0 mL) and ammonium hydroxide (0.5 mL) was sealed and heated to 150 °C in an Emry™  
Creator microwave to 150 °C at 300 watts for 60 minutes. It was then concentrated. The  
25 residue was stirred in water (5 mL) at ambient temperature for 1 hour. The title compound  
was collected by filtration and dried. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 3.12 (s, 6 H), 7.18  
(dd, *J*=5.2, 1.2 Hz, 1 H), 7.21 (t, *J*=1.2 Hz, 1 H), 7.66 - 7.78 (m, 1 H), 8.31 (dd, *J*=4.8, 0.8  
Hz, 1 H), 8.57 (ddd, *J*=8.3, 2.0, 1.6 Hz, 1 H), 8.91 (dd, *J*=5.0, 1.8 Hz, 1 H), 9.35 (d, *J*=2.4 Hz,  
1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 268 (M+H)<sup>+</sup>.

Example 48

3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzoic acid

A solution of the product of Example 45 (180 mg, 0.56 mmol) in methylene chloride (5 mL) was stirred with trifluoroacetic acid (1 mL) at room temperature for 4 hours. It was then concentrated and the residue was stirred in water (15 mL) for 1 hour. The precipitate was collected by filtration and dried to give the title compound. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.66 (ddd, *J*=7.9, 4.8, 0.8 Hz, 1 H), 7.83 (t, *J*=7.5 Hz, 1 H), 8.28 (ddd, *J*=8.0, 1.5, 1.2 Hz, 1 H), 8.42 - 8.51 (m, 2 H), 8.70 (t, *J*=1.6 Hz, 1 H), 8.83 (dd, *J*=5.0, 1.8 Hz, 1 H), 9.28 (dd, *J*=2.2, 1.0 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 268 (M+H)<sup>+</sup>.

#### Example 49

##### 5-(3-(1H-tetrazol-5-yl)phenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole hydrochloric acid

A solution of the product of Example 1 (248 mg, 1.0 mmol) in toluene (anhydrous, 10 mL) was stirred with azidotributylstannane (Aldrich, 498 mg, 1.50 mmol) at 110 °C for 15 hours. It was then cooled to ambient temperature and stirred with 5 mL of sodium hydroxide (1 N) at ambient temperature for 1 hour. The organic solution was separated, the aqueous mixture was acidified to pH = 2-3 with hydrochloric acid (10 wt.%) and stirred for 2 hours. The precipitate was collected by filtration and dried to give the title product. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.70-7.76 (m, 1 H), 7.86 - 7.98 (m, 1 H), 8.23 (ddd, *J*=7.8, 1.7, 1.0 Hz, 0.2 H), 8.38 - 8.46 (m, 1.6 H), 8.49 - 8.53 (m, 0.2 H), 8.56 (ddd, *J*=8.1, 1.9 Hz, 0.8 H), 8.65 (ddd, *J*=1.7, 0.7 Hz, 0.2 H), 8.83 - 8.92 (m, 2 H), 9.30 (dd, *J*=2.2, 0.8 Hz, 0.2 H), 9.33 (dd, *J*=2.2, 0.8 Hz, 0.8 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 292 (M+H)<sup>+</sup>.

#### Example 50

##### *N,N*-diethyl-3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzenesulfonamide

#### Example 50A

##### 3-(*N,N*-diethylsulfamoyl)benzoic acid

Diethylamine (Aldrich, 2.5 mL, 24 mmol) was added to a solution of 3-(chlorosulfonyl)benzoic acid (Aldrich, 2.0 g, 9.1 mmol) in anhydrous dichloromethane (20 mL) at 0 °C. The mixture was then stirred at 0 °C for 2 hours. The volatiles were removed under reduced pressure. The residue was treated with aqueous potassium hydrogensulfate (1 M, 10 mL) and then extracted with ethyl acetate (3x50 mL). The combined extracts were dried over magnesium sulfate filtered and then concentrated to give the title compound. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 1.13 (t, *J*=7.1 Hz, 6 H), 3.22 - 3.30 (m, 4 H), 7.69 (t, *J*=7.8 Hz, 1

H), 8.03 (ddd,  $J=7.9, 1.9, 1.4$  Hz, 1 H), 8.25 (dt,  $J=7.8, 1.4$  Hz, 1 H), 8.40 (t,  $J=1.7$  Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  275 (M+NH<sub>4</sub>)<sup>+</sup>.

#### Example 50B

##### N,N-Diethyl-3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzenesulfonamide

5 The title compound was prepared according to the procedure of Example 8 using *N'*-hydroxynicotinimidamide (Aldrich) and the product of Example 50A. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  1.17 (t,  $J=7.1$  Hz, 6 H), 3.29 - 3.37 (m, 4 H), 7.65 (ddd,  $J=8.1, 5.0, 0.8$  Hz, 1 H), 7.86 (t,  $J=7.6$  Hz, 1 H), 8.14 (ddd,  $J=7.9, 1.8, 1.2$  Hz, 1 H), 8.48 (dt,  $J=7.9, 1.5$  Hz, 1 H), 8.58 (dt,  $J=8.1, 1.9$  Hz, 1 H), 8.62 (t,  $J=1.5$  Hz, 1 H), 8.75 (dd,  $J=5.1, 1.7$  Hz, 1 H), 9.31 (dd,  $J=2.2, 0.8$  Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  359 (M+H)<sup>+</sup>.

#### Example 51

##### 2-fluoro-5-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzonitrile

15 The title compound was prepared according to the procedure of Example 8 using *N'*-hydroxynicotinimidamide (Aldrich) and 3-cyano-4-fluorobenzoic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  ppm 7.62 - 7.71 (m, 2 H), 8.54 - 8.63 (m, 2 H), 8.69 (dd,  $J=5.9, 2.2$  Hz, 1 H), 8.75 (dd,  $J=4.9, 1.5$  Hz, 1 H), 9.30 (dd,  $J=2.0, 1.0$  Hz, 1 H); MS (DCI/NH<sub>3</sub>)  $m/z$  267 (M+H)<sup>+</sup>.

#### Example 52

##### 3-(3-(1H-tetrazol-5-yl)phenyl)-5-(pyridin-3-yl)-1,2,4-oxadiazole hydrochloric acid

20 The title compound was prepared according to the procedure of Example 49 using the product of Example 3 and azidotributylstannane (Aldrich). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.74 (dd,  $J=7.3, 5.4$  Hz, 1 H), 7.87 (t,  $J=7.7$  Hz, 1 H), 8.25 - 8.43 (m, 2 H), 8.53 - 8.70 (m, 1 H), 8.75 - 8.85 (m, 1 H), 8.88 - 9.00 (m, 1 H), 9.32 - 9.58 (m, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  292 (M+H)<sup>+</sup>.

#### Example 53

##### 3-(6-chloropyridin-3-yl)-5-(pyridin-3-yl)-1,2,4-oxadiazole

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#### Example 53A

##### 6-Chloro-*N'*-hydroxynicotinimidamide

A solution of 2-chloroisonicotinonitrile (Aldrich, 5.0 g, 36.1 mmol) and hydroxylamine (Aldrich, 50% wt, 2.38 g, 36.0 mmol) in methanol (100 ml) was heated to reflux and stirred for 1 hour. The volatiles were removed under reduced pressure to give the title compound. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 6.03 (s, 2 H), 7.54 (d, *J*=8.7 Hz, 1 H), 8.07 (dd, *J*=8.3, 2.4 Hz, 1 H), 8.67 (d, *J*=2.8 Hz, 1 H), 9.94 (s, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 172 (M+H)<sup>+</sup>, 189 (M+H)<sup>+</sup>.

#### Example 53B

##### 3-(6-chloropyridin-3-yl)-5-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 1 using the product of Example 53A and nicotinoyl chloride hydrochloride (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.62 - 7.75 (m, 2 H), 8.53 (dd, *J*=8.1, 2.4 Hz, 1 H), 8.60 - 8.67 (m, 1 H), 8.85 (dd, *J*=5.1, 1.7 Hz, 1 H), 9.14 (dd, *J*=2.4, 0.7 Hz, 1 H), 9.39 (dd, *J*=2.2, 0.8 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 259 (M+H)<sup>+</sup>, 261 (M+H)<sup>+</sup>.

#### Example 54

##### 5-(6-chloropyridin-3-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 1 using *N'*-hydroxynicotinimidamide (Tyger) and 6-chloronicotinoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.48 (dd, *J*=7.6, 5.3 Hz, 1 H), 7.57 (d, *J*=8.5 Hz, 1 H), 8.40 - 8.48 (m, 2 H), 8.80 (dd, *J*=4.7, 1.7 Hz, 1 H), 9.24 (d, *J*=2.4 Hz, 1 H), 9.40 (d, *J*=2.4 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 259 (M+H)<sup>+</sup>, 261 (M+H)<sup>+</sup>.

#### Example 55

##### 5-(5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one

A solution of the product of Example 53B (0.10 g, 0.39 mmol) in concentrated hydrochloric acid (1.0 mL) was heated in a microwave to 150 °C at 300 watts for 60 minutes. It was then concentrated under reduced pressure and the residue was purified by chromatography [silica gel, CHCl<sub>3</sub>/methanol (with 10% v/v ammonium hydroxide), v. 90/10] to provide the title compound. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 6.28 - 6.73 (m, 1 H), 7.64 - 7.74 (m, 1 H), 7.98 (dd, *J*=9.5, 2.7 Hz, 1 H), 8.14 (d, *J*=2.4 Hz, 1 H), 8.49 - 8.56 (m, 1 H), 8.89 (dd, *J*=4.7, 1.7 Hz, 1 H), 9.32 (d, *J*=1.4 Hz, 1 H), 12.17 (s, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 241 (M+H)<sup>+</sup>, 258 (M+NH<sub>4</sub>)<sup>+</sup>.

Example 565-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)pyridin-2(1H)-one

The title compound was prepared according to the procedure of Example 55 using the  
5 product of Example 54. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 6.55 (d, *J*=9.2 Hz, 1 H), 7.63 (dd,  
*J*=7.6, 5.3 Hz, 1 H), 8.05 (dd, *J*=9.8, 2.7 Hz, 1 H), 8.31 - 8.47 (m, 2 H), 8.80 (d, *J*=3.4 Hz, 1  
H), 9.22 (s, 1 H), 12.41 (s, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 241 (M+H)<sup>+</sup>, 258 (M+NH<sub>4</sub>)<sup>+</sup>.

Example 57N-methyl-3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzenesulfonamideExample 57A3-(N-methylsulfamoyl)benzoic acid

The title compound was prepared according to the procedure of Example 50A using  
15 3-(chlorosulfonyl)benzoic acid (Aldrich) and methylamine (Aldrich). <sup>1</sup>H NMR (300 MHz,  
CD<sub>3</sub>OD) δ 2.54 (s, 3 H), 7.70 (t, *J*=7.8 Hz, 1 H), 8.02 - 8.07 (m, 1 H), 8.23 - 8.28 (m, 1 H),  
8.45 (t, *J*=1.9 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 233 (M+NH<sub>4</sub>)<sup>+</sup>.

Example 57BN-methyl-3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzenesulfonamide

The title compound was prepared according to the procedure of Example 8 using *N*'-  
20 hydroxynicotinimidamide (Aldrich) and the product of Example 57A. <sup>1</sup>H NMR (300 MHz,  
CD<sub>3</sub>OD) δ 2.60 (s, 3 H), 7.65 (ddd, *J*=8.1, 5.0, 0.8 Hz, 1 H), 7.87 (t, *J*=8.1 Hz, 1 H), 8.15  
(ddd, *J*=8.0, 1.9, 1.0 Hz, 1 H), 8.48 (ddd, *J*=7.8, 1.7, 1.0 Hz, 1 H), 8.58 (dt, *J*=8.1, 1.9 Hz, 1  
25 H), 8.67 (t, *J*=1.5 Hz, 1 H), 8.75 (dd, *J*=4.7, 1.7 Hz, 1 H), 9.31 (dd, *J*=2.2, 0.8 Hz, 1 H) ppm;  
MS (DCI/NH<sub>3</sub>) *m/z* 317 (M+H)<sup>+</sup>.

Example 583-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)aniline dihydrochloride

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Example 58A3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)aniline

The title compound was prepared according to the procedure of Example 46 using the product of Example 40. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ ppm 5.60 (s, 2 H), 6.84 - 6.93 (m, 1 H), 7.24 - 7.33 (m, 2 H), 7.41 (d, *J*=1.7 Hz, 1 H), 7.60 - 7.67 (m, 1 H), 8.38 - 8.45 (m, 1 H), 8.81 (dd, *J*=5.1, 1.7 Hz, 1 H), 9.23 (d, *J*=2.4 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 239 (M+H)<sup>+</sup>, 256 (M+NH<sub>4</sub>)<sup>+</sup>.

#### Example 58B

##### 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)aniline dihydrochloride

A solution of the product of Example 58A (60 mg, 0.25 mmol) in ethyl acetate (2 mL) was stirred with hydrochloric acid (Aldrich, 4 M in dioxane, 0.14 mL, 0.55 mmol) at ambient temperature for 4 hours. The title compound was collected by filtration and dried under vacuum. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.44 (d, *J*=7.9 Hz, 1 H), 7.62 (t, *J*=7.9 Hz, 1 H), 7.80 (dd, *J*=7.9, 5.2 Hz, 1 H), 7.85 - 7.96 (m, 2 H), 8.60 (d, *J*=7.9 Hz, 1 H), 8.90 (d, *J*=4.8 Hz, 1 H), 9.31 (s, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 239 (M+H)<sup>+</sup>, 256 (M+NH<sub>4</sub>)<sup>+</sup>.

#### Example 59

##### (3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenyl)methanamine bis(hydrochloric acid)

A solution of the product of Example 62 (120 mg, 0.34 mmol) in ethyl acetate (5 mL) was stirred with hydrochloric acid (Aldrich, 4 M in dioxane, 0.5 mL, 2.0 mmol) at ambient temperature for 4 hours. The precipitate was collected by filtration and dried under vacuum to give the title compound. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 4.21 (q, *J*=5.9 Hz, 2 H), 7.65 - 7.79 (m, 2 H), 7.86 (dt, *J*=8.0, 1.3 Hz, 1 H), 8.24 (dt, *J*=7.7, 1.4 Hz, 1 H), 8.35 - 8.45 (m, 3 H), 8.48 (dt, *J*=8.1, 1.9 Hz, 1 H), 8.85 (dd, *J*=4.9, 1.2 Hz, 1 H), 9.28 (d, *J*=1.4 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 253 (M+H)<sup>+</sup>.

#### Example 60

##### 5-(2-chloropyridin-4-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 1 using *N*-hydroxynicotinimidamide (Aldrich) and 2-chloroisonicotinoyl chloride (Maybridge). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.68 (ddd, *J*=7.9, 4.8, 0.8 Hz, 1 H), 8.16 (dd, *J*=5.1, 1.4 Hz, 1 H), 8.23 (dd, *J*=1.5, 0.8 Hz, 1 H), 8.42 - 8.54 (m, 1 H), 8.77 (dd, *J*=5.1, 0.7 Hz, 1 H), 8.84 (dd, *J*=4.7, 1.7 Hz, 1 H), 9.28 (dd, *J*=2.2, 0.8 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 259 (M+H)<sup>+</sup>, 261 (M+H)<sup>+</sup>.

Example 614-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)pyridin-2(1H)-one hydrochloric acid

The title compound was prepared according to the procedure of Example 44 using the  
5 product of Example 60. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 6.81 (dd, *J*=6.6, 1.9 Hz, 1 H), 7.09  
- 7.14 (m, 1 H), 7.67 - 7.76 (m, 2 H), 8.51 (dt, *J*=8.0, 1.9, 1.7 Hz, 1 H), 8.86 (dd, *J*=4.9, 1.5  
Hz, 1 H), 9.28 (d, *J*=1.4 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 241 (M+H)<sup>+</sup>.

Example 62tert-butyl 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzylcarbamate

The title compound was prepared according to the procedure of Example 8 using *N*-  
10 hydroxynicotinimidamide (Aldrich) and 3-((tert-butoxycarbonylamino)methyl)benzoic acid  
(Fluka). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.42 (s, 9 H), 4.27 (d, *J*=6.1 Hz, 2 H), 7.51 - 7.72  
(m, 4 H), 8.01 - 8.17 (m, 2 H), 8.45 (dt, *J*=8.1, 1.9 Hz, 1 H), 8.82 (dd, *J*=5.1, 1.7 Hz, 1 H),  
15 9.26 (dd, *J*=2.2, 0.8 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 353 (M+H)<sup>+</sup>.

Example 635-(3-bromophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 1 using *N*-  
20 hydroxynicotinimidamide (Aldrich) and 3-bromobenzoyl chloride (Aldrich). <sup>1</sup>H NMR (300  
MHz, DMSO-*d*<sub>6</sub>) δ 7.60 - 7.71 (m, 2 H), 7.98 (ddd, *J*=8.1, 2.0, 1.0 Hz, 1 H), 8.22 (ddd, *J*=7.4,  
1.6, 1.3 Hz, 1 H), 8.35 (t, *J*=1.8 Hz, 1 H), 8.46 (dt, *J*=7.9, 2.0 Hz, 1 H), 8.83 (dd, *J*=4.8, 1.6  
Hz, 1 H), 9.27 (dd, *J*=2.4, 0.8 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 302 (M+H)<sup>+</sup>, 304 (M+H)<sup>+</sup>.

Example 641-(3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenyl)pyrrolidin-2-one

A solution of the product of Example 63 (200mg, 0.66 mmol) and pyrrolidin-2-one  
(Aldrich, 85 mg, 0.99 mmol) in toluene (anhydrous 10 mL) was degassed and purged with  
nitrogen three times, cesium carbonate (Aldrich, 324 mg, 0.993 mmol) and  
30 tris(dibenzylideneacetone)dipalladium(0) (Aldrich, 12.1 mg, 0.013 mmol), 4,5-  
bis(diphenylphosphino)-9,9-dimethylxanthene (Aldrich, 23.0 mg, 0.040 mmol, xantphos)  
were added, degassed and purged with nitrogen three times. The mixture was then heated to  
100 °C and stirred under nitrogen for 15 hours. It was then cooled to ambient temperature  
and diluted with ethyl acetate (50 mL), washed with brine (2 x 5 mL), concentrated, purified

with chromatography (v. ethyl acetate/hexane = 1/1,  $R_f=0.1$ ) to give the title compound.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-}d_6$ )  $\delta$  2.04 - 2.19 (m, 2 H), 2.57 (t,  $J=7.9$  Hz, 2 H), 3.95 (t,  $J=6.9$  Hz, 2 H), 7.60 - 7.75 (m, 2 H), 7.84 - 8.10 (m, 2 H), 8.46 (dt,  $J=7.9, 2.0$  Hz, 1 H), 8.64 (t,  $J=2.0$  Hz, 1 H), 8.82 (dd,  $J=5.0, 1.8$  Hz, 1 H), 9.26 (dd,  $J=2.4, 0.8$  Hz, 1 H) ppm; MS (DCI/ $\text{NH}_3$ )  $m/z$  307 ( $\text{M}+\text{H}$ ) $^+$ .

#### Example 65

##### tert-butyl 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenylcarbamate

The title compound was prepared according to the procedure of Example 8 using  $N'$ -hydroxynicotinimidamide (Aldrich) and 3-(*tert*-butoxycarbonylamino)benzoic acid (Aldrich).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.56 (s, 9 H), 6.71 (s, 1 H), 7.39 - 7.58 (m, 2 H), 7.68 (d,  $J=7.9$  Hz, 1 H), 7.89 (d,  $J=9.1$  Hz, 1 H), 8.24 (s, 1 H), 8.45 (d,  $J=7.9$  Hz, 1 H), 8.77 (d,  $J=4.8$  Hz, 1 H), 9.40 (s, 1 H) ppm; MS (DCI/ $\text{NH}_3$ )  $m/z$  339 ( $\text{M}+\text{H}$ ) $^+$ , 356 ( $\text{M}+\text{NH}_4$ ) $^+$ .

#### Example 66

##### N,N-dimethyl-1-(3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenyl)methanamine, bishydrochloric acid salt

The free base of the title compound was prepared according to the procedure of Example 8 using  $N'$ -hydroxynicotinimidamide (Aldrich) and 3-((dimethylamino)methyl)benzoic acid (Aldrich). A solution of this free base in ethyl acetate (5 mL) was treated with hydrochloric acid (Aldrich, 0.5 mL, 4M in dioxane) at ambient temperature for 2 hours. The title compound was collected by filtration and dried under vacuum.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  2.93 (s, 6 H), 4.51 (s, 2 H), 7.82 (t,  $J=7.8$  Hz, 1 H), 7.90 (dt,  $J=7.8, 1.5$  Hz, 1 H), 8.23 (dd,  $J=8.0, 5.9$  Hz, 1 H), 8.42 (dt,  $J=7.7, 1.4$  Hz, 1 H), 8.49 (t,  $J=1.5$  Hz, 1 H), 9.04 (d,  $J=5.1$  Hz, 1 H), 9.21 (dt,  $J=8.1, 1.7$  Hz, 1 H), 9.56 (s, 1 H) ppm; MS (DCI/ $\text{NH}_3$ )  $m/z$  281 ( $\text{M}+\text{H}$ ) $^+$ .

#### Example 67

##### 5-(3-(piperazin-1-yl)phenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole bis(hydrochloric acid)

#### Example 67A

##### tert-butyl 4-(3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenyl)piperazine-1-carboxylate

A solution of the product of Example 63 (200mg, 0.66 mmol) and tert-butyl piperazine-1-carboxylate (Aldrich, 123 mg, 0.66 mmol) in toluene (anhydrous, 10 mL) was degassed and purged with nitrogen three times, sodium t-butoxide (Aldrich, 64 mg, 0.66 mmol) and tris(dibenzylideneacetone)dipalladium(0) (Aldrich, 12.1 mg, 0.013 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Aldrich, 23.0 mg, 0.040 mmol, xantphos) were added, degassed and purged with nitrogen three times. The mixture was then heated to 100 °C and stirred under nitrogen for 15 hours. It was then cooled to ambient temperature and diluted with ethyl acetate (50 mL), washed with brine (2 x 5 mL), concentrated, purified with chromatography (v. ethyl acetate/hexane = 1/1,  $R_f=0.6$ ) to give the title compound.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  1.49 (s, 9 H), 3.25 - 3.30 (m, 4 H), 3.56 - 3.71 (m, 4 H), 7.31 (ddd,  $J=8.4, 2.6, 0.8$  Hz, 1 H), 7.49 (t,  $J=8.0$  Hz, 1 H), 7.64 (ddd,  $J=8.0, 4.9, 0.7$  Hz, 1 H), 7.70 (dt,  $J=8.0, 1.1$  Hz, 1 H), 7.79 (dd,  $J=2.4, 1.7$  Hz, 1 H), 8.56 (dt,  $J=7.9, 2.0$  Hz, 1 H), 8.74 (dd,  $J=4.9, 1.5$  Hz, 1 H), 9.29 (dd,  $J=2.2, 0.8$  Hz, 1 H) ppm; MS (DCI/ $\text{NH}_3$ )  $m/z$  408 (M+H) $^+$ .

#### Example 67B

##### 5-(3-(piperazin-1-yl)phenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole bis(hydrochloric acid)

The title compound was prepared according to the procedure of Example 59 using the product of Example 67A.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  3.40 - 3.48 (m, 4 H), 3.54 - 3.62 (m, 4 H), 7.42 (ddd,  $J=8.3, 2.8, 0.8$  Hz, 1 H), 7.58 (t,  $J=8.1$  Hz, 1 H), 7.78 - 7.94 (m, 2 H), 8.24 - 8.39 (m, 1 H), 9.08 (d,  $J=5.9$  Hz, 1 H), 9.32 (dt,  $J=8.3, 1.8$  Hz, 1 H), 9.59 (d,  $J=1.6$  Hz, 1 H) ppm; MS (DCI/ $\text{NH}_3$ )  $m/z$  308 (M+H) $^+$ .

#### Example 68

##### 1-(3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenyl)ethanone

The title compound was prepared according to the procedure of Example 8 using N'-hydroxynicotinimidamide (Aldrich) and 3-acetylbenzoic acid (Aldrich).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  2.72 (s, 3 H), 7.66 (ddd,  $J=8.0, 4.9, 1.0$  Hz, 1 H), 7.80 (t,  $J=8.1$  Hz, 1 H), 8.31 (ddd,  $J=8.1, 1.4, 1.2$  Hz, 1 H), 8.47 (ddd,  $J=8.1, 1.4, 1.2$  Hz, 1 H), 8.59 (ddd,  $J=8.1, 2.0, 1.8$  Hz, 1 H), 8.75 (dd,  $J=5.2, 1.6$  Hz, 1 H), 8.81 (t,  $J=1.4$  Hz, 1 H), 9.32 (dd,  $J=2.4, 0.8$  Hz, 1 H) ppm; MS (DCI/ $\text{NH}_3$ )  $m/z$  266 (M+H) $^+$ .

#### Example 69

##### 3-(6-chloropyridin-3-yl)-5-(2,3-difluorophenyl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 1 using the product of Example 53A and 2,3-difluorobenzoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.41 - 7.59 (m, 1 H), 7.76 - 7.93 (m, 2 H), 8.05 (dd, *J*=7.8, 6.1 Hz, 1 H), 8.48 (dd, *J*=8.3, 2.5 Hz, 1 H), 9.08 (d, *J*=2.4 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 294 (M+H)<sup>+</sup>, 296 (M+H)<sup>+</sup>.

#### Example 70

##### 3-(6-chloropyridin-3-yl)-5-(3,4-difluorophenyl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 1 using the product of Example 53A and 3,4-difluorobenzoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ ppm 7.70 - 7.83 (m, 2 H), 8.03 - 8.15 (m, 1 H), 8.22 - 8.36 (m, 1 H), 8.48 (dd, *J*=8.1, 2.4 Hz, 1 H), 9.08 (d, *J*=2.4 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 294 (M+H)<sup>+</sup>, 296 (M+H)<sup>+</sup>.

#### Example 71

##### (R)-3-(pyridin-3-yl)-5-(3-(pyrrolidin-2-yl)phenyl)-1,2,4-oxadiazole bis(hydrochloric acid)

#### Example 71A

##### (R)-tert-butyl 2-(3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenyl)pyrrolidine-1-carboxylate

Under nitrogen, to a solution of tert-butyl pyrrolidine-1-carboxylate (Aldrich, 0.52 g, 3.00 mmol) and (-)-sparteine (Aldrich, 0.69 g, 3.0 mmol) in *t*-butyl methyl ether (Aldrich, anhydrous, 10 mL) was added *sec*-butyllithium (Aldrich, 1.4 M in cyclohexane, 2.2 mL, 3.1 mmol) at -78 °C. After the completion of the addition, it was stirred at -78 °C for 3 hours. Zinc chloride (Aldrich, 1 M in diethyl ether, 2.0 mL, 2.0 mmol) was then added slowly and the resultant solution was stirred at -78 °C for additional 30 minutes and then warmed up to ambient temperature, stirred for another 30 minutes at room temperature before the addition of a solution of the product of the Example 63 (0.30 g, 1.0 mmol) in tetrahydrofuran (anhydrous, 5.0 mL) and bis(tri-*t*-butylphosphine)palladium(0) (Strem, 10.2 mg, 0.02 mmol). The mixture was stirred at ambient temperature for 15 hours and quenched with ammonium hydroxide (5 mL). The mixture was extracted with ethyl acetate (3 x 20 mL). The combined extracts were concentrated and purified by chromatography (v. hexanes/ethyl acetate = 1/1, *R<sub>f</sub>*=0.5) to give the title compound. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 1.19 (s (broad), 6 H), 1.48 (s (broad), 3 H), 1.83 - 2.00 (m, 2 H), 2.37 - 2.55 (m, *J*=8.1, 8.1 Hz, 1 H), 3.57 - 3.72 (m,

2 H), 4.90 - 5.14 (m, 1 H), 7.47 - 7.73 (m, 3 H), 8.00 - 8.25 (m, 2 H), 8.56 (dt,  $J=8.3$ , 1.8 Hz, 1 H), 8.74 (dd,  $J=5.1$ , 1.7 Hz, 1 H), 9.29 (dd,  $J=2.0$ , 0.7 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  393 (M+H)<sup>+</sup>.

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#### Example 71B

##### (R)-3-(Pyridin-3-yl)-5-(3-(pyrrolidin-2-yl)phenyl)-1,2,4-oxadiazole bis(hydrochloric acid)

The title compound was prepared according to the procedure of Example 59 using the product of Example 71A. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  1.98 - 2.27 (m, 3 H), 2.39 - 2.50 (m, 1 H), 3.22 - 3.51 (m, 2 H), 4.55 - 4.81 (m, 1 H), 7.71 - 7.82 (m, 2 H), 7.96 (d,  $J=7.9$  Hz, 1 H), 8.26 (dt,  $J=7.8$ , 1.2 Hz, 1 H), 8.40 (s, 1 H), 8.58 (dt,  $J=8.1$ , 1.9 Hz, 1 H), 8.89 (dd,  $J=5.2$ , 1.6 Hz, 1 H), 9.21 - 9.53 (m,  $J=1.6$  Hz, 2 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  293 (M+H)<sup>+</sup>.

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#### Example 72

##### 5-(3-(1H-pyrazol-3-yl)phenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to the procedure of Example 8 using *N*-hydroxynicotinimidamide (Aldrich) and 3-(1H-pyrazol-3-yl)benzoic acid (Maybridge). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  6.91 (d,  $J=2.4$  Hz, 1 H), 7.62 - 7.69 (m, 1 H), 7.72 (t,  $J=7.8$  Hz, 1 H), 7.79 - 7.92 (m, 1 H), 7.82-7.88 (m, 1H), 8.10-8.20 (m, 3 H), 8.49 (dt,  $J=8.2$ , 1.9, 1.7 Hz, 1 H), 8.64 (s, 1 H), 8.83 (dd,  $J=4.7$ , 1.7 Hz, 1 H), 9.29 (dd,  $J=2.2$ , 0.8 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  290 (M+H)<sup>+</sup>.

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#### Example 73

##### 1-(3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenyl)ethanol

A solution of the product of Example 68 (265 mg, 1.0 mmol) in ethanol (5 mL) was stirred with sodium borohydride (Aldrich, 83 mg, 2.2 mmol) at room temperature for 16 hours. The inorganic solid was filtered off with a syringe filter and the liquid mixture was purified by preparative HPLC (Gilson, column, Xbridge<sup>®</sup> 5  $\mu$ m, 30 x 100 mm. eluting solvent, acetonitrile/water (pH = 10, NH<sub>4</sub>HCO<sub>3</sub>-NH<sub>3</sub>•H<sub>2</sub>O buffer), v. 5/95 to 95/5 over 35 minutes, flow rate, 40 mL/minute, uv, 234 nm). Fractions of the desired product were collected and concentrated to give the desired product. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  1.51 (d,  $J=6.7$  Hz, 3 H), 4.97 (q,  $J=6.6$  Hz, 1 H), 7.57 - 7.73 (m, 3 H), 8.13 (dt,  $J=7.6$ , 1.5 Hz, 1 H), 8.28 (t,  $J=1.8$  Hz, 1 H), 8.57 (dt,  $J=7.9$ , 1.8 Hz, 1 H), 8.74 (dd,  $J=5.0$ , 1.8 Hz, 1 H), 9.30 (dd,  $J=2.2$ , 1.0 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  268 (M+H)<sup>+</sup>.

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Example 743-(3-(6-chloropyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile

The title compound was prepared according to the procedure of Example 1 using the product of Example 53A and 3-cyanobenzoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.52 (d, J=7.8 Hz, 1 H), 7.75 (t, J=8.0 Hz, 1 H), 7.93 (d, J=7.8 Hz, 1 H), 8.30 - 8.50 (m, 2 H), 8.54 (s, 1 H), 9.19 (d, J=2.4 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) m/z 283 (M+H)<sup>+</sup>, 300 (M+NH<sub>4</sub>)<sup>+</sup>.

Example 753-(4-fluorophenyl)-5-(pyridin-3-yl)-1,2,4-oxadiazole

4-Fluoro-N<sup>1</sup>-hydroxybenzimidamide (0.154 g, 1 mmol) was dissolved in pyridine (10 mL) and nicotinoyl chloride (Aldrich, 0.141 g, 1 mmol) was added. The reaction mixture was heated to reflux for 3 hours and then cooled to room temperature. The cooled reaction mixture was quenched with water (25 mL) and filtered. The solid was further purified with flash column chromatography (5% methanol/dichloromethane) to give the titled product. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.47 (t, J= 6.8 Hz, 2 H), 7.74-7.70 (m, 1 H), 8.20-8.15 (m, 2 H), 8.58-8.54 (m, 1 H), 8.91-8.89 (dd, J= 1.7,1.7 Hz, 1 H), 9.35 (d, J= 1.4 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) m/z 242 (M+H)<sup>+</sup>.

Example 763-(5-(6-chloropyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzotrile

The title compound was prepared according to the procedure of Example 4B using 3-cyano-N<sup>1</sup>-hydroxybenzimidamide (Example 4A) and 6-chloronicotinoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.87 (m, 2 H), 8.17 (m, 1 H), 8.4 (m, 1 H), 8.43 (d, J=1.7 Hz, 1 H), 8.6 (m, 1 H), 9.25 (d, J=1.7 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) m/z 283 (M+H)<sup>+</sup>.

Example 773-(5-(2-fluoropyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzotrile

The title compound was prepared according to the procedure of Example 4B using 3-cyano-N<sup>1</sup>-hydroxybenzimidamide (Example 4A) and 2-fluoronicotinoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.87 (m, 1 H), 7.95 (m, 1 H), 8.17 (m, 1 H), 8.17 (m, 1 H), 8.43 (m, 1 H), 8.6 (m, 1 H), 8.8 (m, 1 H) ppm; MS (DCI/NH<sub>3</sub>) m/z 267 (M+H)<sup>+</sup>.

Example 783-fluoro-5-(5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzotrile

5 The title compound was prepared according to the procedure of Example 4B using 3-cyano-5-fluoro-N'-hydroxybenzimidamide (Prepared from 5-fluoroisophthalonitrile using the procedure described in Example 4A.) and nicotinoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.77 (m, 1 H), 8.2 (m, 2 H), 8.4 (m, 1 H), 8.6 (m, 1 H), 8.9 (m, 1 H), 9.4 (m, 1 H) ppm; MS (DCI/NH<sub>3</sub>) m/z 267 (M+H)<sup>+</sup>.

Example 795-(2,3-Difluorophenyl)-3-(pyrimidin-5-yl)-1,2,4-oxadiazoleExample 79APyrimidine-5-carboxamide

15 A solution of ethyl pyrimidine-5-carboxylate (6.10 g, 40.0 mmol) in methanol (40 mL) was stirred with ammonium hydroxide (4.30 mL, 110 mmol) in a sealed tube at 50 °C for 10 hours. The reaction mixture was then concentrated and the residue was stirred in ethanol/ethyl acetate (v/v 1/4, 50 mL) at ambient temperature for 2 hours. The white precipitate was collected by filtration and dried to give the titled compound. <sup>1</sup>H NMR (300  
20 MHz, DMSO-*d*<sub>6</sub>) δ 7.85 [s (broad), 1 H], 8.33 [s (broad), 1 H], 9.18 (s, 2 H), 9.32 (s, 1 H) ppm; MS (DCI/NH<sub>3</sub>) m/z 124 (M+H)<sup>+</sup>, 141 (M+NH<sub>4</sub>)<sup>+</sup>.

Example 79BPyrimidine-5-carbonitrile

25 To a suspension of the product of Example 79A (6.75 g, 54.8 mmol) and triethylamine (Aldrich, 15.28 mL, 110 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (Aldrich, 400 mL) was slowly added a solution of trifluoroacetic anhydride (Aldrich, 9.30 mL, 65.8 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (100 mL) at 0–10 °C over 1 hours. It was then stirred at 0 °C to ambient  
30 temperature for 2 hours. The reaction was then quenched with water (10 mL) and washed with NaOH (1 N, 20 mL) and brine (2 x 10 mL) before being concentrated under reduced pressure at less than 30 °C to supply the titled compound. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 9.34 (s, 2 H), 9.47 (s, 1 H) ppm; MS (DCI/NH<sub>3</sub>) m/z 123 (M+NH<sub>4</sub>)<sup>+</sup>.

Example 79C*N'*-Hydroxypyrimidine-5-carboximidamide

A solution of the product of Example 79B (5.47 g, 52 mmol) and aqueous hydroxylamine (Aldrich, 50%, 2.3 mL, 78 mmol) in methanol (50 mL) was stirred at 65 °C for 1 hour and then concentrated under reduced pressure to remove the volatiles. The residue was triturated with EtOAc (30 mL). The precipitates were collected by filtration and dried to give the titled compound. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 6.14 (s, 2 H), 9.03 (s, 2 H), 9.18 (s, 1 H), 10.06 (s, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 139 (M+H)<sup>+</sup>, 156 (M+NH<sub>4</sub>)<sup>+</sup>.

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Example 79D5-(2,3-Difluorophenyl)-3-(pyrimidin-5-yl)-1,2,4-oxadiazole

The titled compound was prepared according to the procedure of Method D using the product of Example 79C and 2,3-difluorobenzoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.27 - 7.39 (m, 1 H), 7.42 - 7.56 (m, 1 H), 7.95 - 8.08 (m, 1 H), 9.39 (s, 1 H), 9.49 (s, 2 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 261 (M+H)<sup>+</sup>.

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Example 805-(pyridin-3-yl)-3-(pyrimidin-5-yl)-1,2,4-oxadiazole

The titled compound was prepared according to the procedure of Method D using the product of Example 79C and nicotinoyl chloride hydrochloride (Aldrich). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.74 (ddd, *J*=8.0, 4.9, 0.7 Hz, 1 H), 8.54 - 8.64 (m, 1 H), 8.93 (dd, *J*=4.9, 1.5 Hz, 1 H), 9.39 (d, *J*=1.7 Hz, 1 H), 9.45 (s, 1 H), 9.46 (s, 2 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 226 (M+H)<sup>+</sup>.

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Example 812-fluoro-*N,N*-dimethyl-4-(3-(pyrimidin-5-yl)-1,2,4-oxadiazol-5-yl)aniline

The titled compound was prepared according to the procedure of Method C using the product of Example 79C and 3,4-difluorobenzoic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 3.06 (s, 3 H), 3.07 (s, 3 H), 6.89 (t, *J*=8.7 Hz, 1 H), 7.76 - 7.96 (m, 2 H), 9.36 (s, 1 H), 9.43 - 9.47 (m, 2 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 286 (M+H)<sup>+</sup>.

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Example 823-(3-(pyrimidin-5-yl)-1,2,4-oxadiazol-5-yl)benzotrile

The titled compound was prepared according to the procedure of Method D using the product of Example 79C and 3-cyanobenzoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.91 (t, *J*=7.9 Hz, 1 H), 8.24 (dt, *J*=7.7, 1.4, 1.2 Hz, 1 H), 8.53 (dt, *J*=8.1, 1.4, 1.2 Hz, 1 H), 8.67 (t, *J*=1.8 Hz, 1 H), 9.45 (s, 1 H), 9.46 (s, 2 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 250 (M+H)<sup>+</sup>.

Example 835-(3,4-Difluorophenyl)-3-(pyridazin-4-yl)-1,2,4-oxadiazole hydrochlorideExample 83AMethyl pyridazine-4-carboxylate

To a solution of pyridazine-4-carboxylic acid (Aldrich, 5.0 g, 40.3 mmol) in methanol (anhydrous, Aldrich, 100 mL) was added sulfuric acid (concentrated, Aldrich, 2 mL). The reaction mixture was then heated to reflux and stirred for 16 hours. The volatiles were removed under reduced pressure. The residue was basified to pH= 8-9 with saturated sodium carbonate (20 mL) and then extracted with EtOAc (3 x 100 mL). The combined extracts were washed with brine (2 x 20 mL) and dried over magnesium sulfate. The drying agent was filtered off and the organic solution was concentrated and dried to give the titled compound. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 3.34 (s, 3 H), 8.10 (dd, *J*=5.2, 2.4 Hz, 1 H), 9.52 (dd, *J*=5.2, 1.2 Hz, 1 H), 9.58 (dd, *J*=2.2, 1.4 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 139 (M+H)<sup>+</sup>.

Example 83Bpyridazine-4-carboxamide

The title compound was prepared according to the procedure of Example 79A using the product of Example 83A and ammonium hydroxide (Aldrich). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 8.00 (dd, *J*=5.2, 2.4 Hz, 1 H), 8.46 [s (broad), 2 H], 9.44 (dd, *J*=5.2, 1.2 Hz, 1 H), 9.55 (dd, *J*=2.2, 1.4 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 124 (M+H)<sup>+</sup>, 141 (M+NH<sub>4</sub>)<sup>+</sup>.

Example 83C

pyridazine-4-carbonitrile

The title compound was prepared according to the procedure of Example 79B using the product of Example 83B and trifluoroacetic anhydride (Aldrich). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 8.28 (dd, *J*=5.4, 2.2 Hz, 1 H), 9.57 (dd, *J*=5.2, 1.2 Hz, 1 H), 9.66 (dd, *J*=2.2, 1.4 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 123 (M+NH<sub>4</sub>)<sup>+</sup>.

Example 83D

*N'*-Hydroxypyridazine-4-carboximidamide

The title compound was prepared according to the procedure of Example 79C using the product of Example 83C and hydroxylamine (Aldrich). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 6.19 (s, 2 H), 7.87 (dd, *J*=5.4, 2.4 Hz, 1 H), 9.25 (dd, *J*=5.4, 1.4 Hz, 1 H), 9.46 (dd, *J*=2.4, 1.4 Hz, 1 H), 10.36 (s, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 139 (M+H)<sup>+</sup>, 156 (M+NH<sub>4</sub>)<sup>+</sup>.

Example 83E

5-(3,4-difluorophenyl)-3-(pyridazin-4-yl)-1,2,4-oxadiazole

The titled compound was prepared according to the procedure of Method D using the product of Example 83D and 3,4-difluorobenzoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.80 (dt, *J*=10.5, 8.3 Hz, 1 H), 8.08 - 8.19 (m, 1 H), 8.29 (dd, *J*=5.4, 2.4 Hz, 1 H), 8.31 - 8.38 (m, 1 H), 9.55 (dd, *J*=5.4, 1.4 Hz, 1 H), 9.82 (dd, *J*=2.2, 1.2 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 261 (M+H)<sup>+</sup>.

Example 83F

5-(3,4-Difluorophenyl)-3-(pyridazin-4-yl)-1,2,4-oxadiazole hydrochloride

A solution of the product of Example 83E (140 mg, 0.54 mmol) in ethyl acetate (5.0 mL) was stirred with hydrochloric acid (Aldrich, 4 M in dioxane, 0.25 mL, 1.0 mmol) at ambient temperature for 10 hours. The white precipitates were collected by filtration and dried to give the title compound. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.81 (dt, *J*=10.5, 8.5 Hz, 1 H), 8.08 - 8.19 (m, 1 H), 8.26 - 8.39 (m, 2 H), 9.55 (dd, *J*=5.4, 1.4 Hz, 1 H), 9.83 (dd, *J*=2.4, 1.4 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 261 (M+H)<sup>+</sup>.

Example 84

3-(Pyridazin-4-yl)-5-(pyridin-3-yl)-1,2,4-oxadiazole

The titled compound was prepared according to the procedure of Method D using the product of Example 83D and nicotinoyl chloride hydrochloride (Aldrich). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.75 (ddd, *J*=8.0, 4.9, 0.7 Hz, 1 H), 8.32 (dd, *J*=5.3, 2.2 Hz, 1 H), 8.61 (dt, *J*=8.2, 1.8 Hz, 1 H), 8.93 (dd, *J*=5.1, 1.7 Hz, 1 H), 9.39 (dd, *J*=2.2, 0.8 Hz, 1 H), 9.55 (dd, *J*=5.4, 1.4 Hz, 1 H), 9.85 (dd, *J*=2.2, 1.2 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 226 (M+H)<sup>+</sup>.

#### Example 85

*N,N*-Dimethyl-*N'*-(4-(3-(pyrimidin-5-yl)-1,2,4-oxadiazol-5-yl)phenylsulfonyl)formimidamide

The titled compound was prepared according to the procedure of Method D using the product of Example 79C and 4-sulfamidobenzoyl chloride dimethylformamide complex (Alfa Aesar). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 2.94 (s, 3 H), 3.18 (s, 3 H), 8.06 (d, *J*=8.8 Hz, 2 H), 8.30 (s, 1 H), 8.37 (d, *J*=8.8 Hz, 2 H), 9.45 (s, 1H), 9.46 (s, 2 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z*= 359 (M+H)<sup>+</sup>, 376 (M+NH<sub>4</sub>)<sup>+</sup>.

#### Example 86

5-(4-fluorophenyl)-3-(pyrimidin-5-yl)-1,2,4-oxadiazole

The titled compound was prepared according to the procedure of Method D using the product of Example 79C and 4-fluorobenzoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.51 – 7.59 (m, 2 H), 8.27 - 8.34 (m, 2 H), 9.44 (s, 2 H), 9.45 (S, 1H) ppm; MS (DCI/NH<sub>3</sub>) *m/z*= 243 (M+H)<sup>+</sup>, 260 (M+NH<sub>4</sub>)<sup>+</sup>.

#### Example 87

5-(3-fluorophenyl)-3-(pyrimidin-5-yl)-1,2,4-oxadiazole

The titled compound was prepared according to the procedure of Method D using the product of Example 79C and 3-fluorobenzoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.61 - 7.71 (m, 1 H), 7.72 - 7.84 (m, 1 H), 8.04 (ddd, *J*=9.3, 2.5, 1.4 Hz, 1 H), 8.07 - 8.12 (m, 1 H), 9.45 (s, 3 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z*= 243 (M+H)<sup>+</sup>, 260 (M+NH<sub>4</sub>)<sup>+</sup>.

#### Example 88

3-(pyrimidin-5-yl)-5-(3,4,5-trifluorophenyl)-1,2,4-oxadiazole

The titled compound was prepared according to the procedure of Method D using the product of Example 79C and 3,4,5-trifluorobenzoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz,

DMSO- $d_6$ )  $\delta$  8.24 (dd,  $J=8.0, 6.6$  Hz, 2 H), 9.44 (s, 2 H), 9.46 (s, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z= 279$  (M+H)<sup>+</sup>, 296 (M+NH<sub>4</sub>)<sup>+</sup>.

#### Example 89

5                    5-(2-Chloropyridin-4-yl)-3-(pyrimidin-5-yl)-1,2,4-oxadiazole

The titled compound was prepared according to the procedure of Method D using the product of Example 79C and 2-chloroisonicotinoyl chloride (Maybridge). <sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.17 (dd,  $J=5.1, 1.4$  Hz, 1 H), 8.25 (dd,  $J=1.4, 0.7$  Hz, 1 H), 8.78 (dd,  $J=5.1, 0.7$  Hz, 1 H), 9.46 (s, 1 H), 9.47 (s, 2 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z= 260$  (M+H)<sup>+</sup>, 262 (M+H)<sup>+</sup>.

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#### Example 90

3-(Pyridin-3-yl)-5-(pyrimidin-5-yl)-1,2,4-oxadiazole

The titled compound was prepared according to the procedure of Method C using *N'*-hydroxynicotinimidamide (Tyger) and pyrimidine-5-carboxylic acid (Maybridge). <sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ )  $\delta$  7.68 (ddd,  $J=8.0, 4.9, 1.0$  Hz, 1 H), 8.48 (dt,  $J=7.7, 2.1$  Hz, 1 H), 8.84 (dd,  $J=4.7, 1.7$  Hz, 1 H), 9.29 (dd,  $J=2.4, 1.0$  Hz, 1 H), 9.51 (s, 1 H), 9.56 (s, 2 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z= 226$  (M+H)<sup>+</sup>, 243 (M+NH<sub>4</sub>)<sup>+</sup>.

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Example 915-(Pyridazin-4-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The titled compound was prepared according to the procedure of Method C using N'-hydroxynicotinimidamide (Aldrich) and pyridazine-4-carboxylic acid (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.67 (ddd, *J*=8.1, 5.0, 0.8 Hz, 1 H), 8.45 (dd, *J*=5.4, 2.4 Hz, 1 H), 8.60 (dt, *J*=8.1, 1.9 Hz, 1 H), 8.78 (dd, *J*=5.1, 1.7 Hz, 1 H), 9.34 (dd, *J*=2.2, 0.8 Hz, 1 H), 9.55 (dd, *J*=5.4, 1.4 Hz, 1 H), 9.94 (dd, *J*=2.2, 1.2 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z*= 226 (M+H)<sup>+</sup>.

Example 923-(3-(Pyridazin-4-yl)-1,2,4-oxadiazol-5-yl)benzotrile

The titled compound was prepared according to the procedure of Method D using the product of Example 83D and 3-cyanobenzoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.86 (t, *J*=7.9 Hz, 1 H), 8.09 (ddd, *J*=8.1, 1.4, 1.2 Hz, 1 H), 8.40 (dd, *J*=5.4, 2.2 Hz, 1 H), 8.55 (dt, *J*=7.9, 1.6 Hz, 1 H), 8.64 (t, *J*=2.0 Hz, 1 H), 9.46 (dd, *J*=5.4, 1.4 Hz, 1 H), 9.88 (dd, *J*=2.2, 1.4 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z*= 250 (M+H)<sup>+</sup>.

Example 93

5-(3-Fluorophenyl)-3-(pyridazin-4-yl)-1,2,4-oxadiazoleThe titled compound was prepared according to the procedure of Method D using the product of Example 83D and 3-fluorobenzoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.45 - 7.53 (m, 1 H), 7.69 (td, *J*=8.1, 5.6 Hz, 1 H), 8.00 (ddd, *J*=9.1, 2.6, 1.4 Hz, 1 H), 8.11 (dt, *J*=7.9, 1.2 Hz, 1 H), 8.39 (dd, *J*=5.4, 2.2 Hz, 1 H), 9.45 (dd, *J*=5.2, 1.2 Hz, 1 H), 9.87 (dd, *J*=2.2, 1.4 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z*= 243 (M+H)<sup>+</sup>.

Example 943-(Pyridazin-4-yl)-5-(3,4,5-trifluorophenyl)-1,2,4-oxadiazole

The titled compound was prepared according to the procedure of Method D using the product of Example 83D and 3,4,5-trifluorobenzoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 8.04 - 8.16 (m, 2 H), 8.38 (dd, *J*=5.4, 2.2 Hz, 1 H), 9.46 (dd, *J*=5.4, 1.4 Hz, 1 H), 9.86 (dd, *J*=2.4, 1.2 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z*= 279 (M+H)<sup>+</sup>.

Example 955-(3,5-difluorophenyl)-3-(pyridazin-4-yl)-1,2,4-oxadiazole

The titled compound was prepared according to the procedure of Method D using the product of Example 83D and 3,5-difluorobenzoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.40 (tt, *J*=8.9, 2.4 Hz, 1 H), 7.85 - 7.94 (m, 2 H), 8.39 (dd, *J*=5.4, 2.2 Hz, 1 H), 9.46 (dd, *J*=5.4, 1.4 Hz, 1 H), 9.87 (dd, *J*=2.2, 1.4 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z*= 261 (M+H)<sup>+</sup>.

Example 965-(4-fluorophenyl)-3-(pyridazin-4-yl)-1,2,4-oxadiazole

The titled compound was prepared according to the procedure of Method D using the product of Example 83D and 4-fluorobenzoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.36 - 7.45 (m, 2 H), 8.29 - 8.40 (m, 3 H), 9.45 (dd, *J*=5.6, 1.2 Hz, 1 H), 9.86 (dd, *J*=2.4, 1.2 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z*= 243 (M+H)<sup>+</sup>.

Example 973-(pyridazin-4-yl)-5-(pyrimidin-5-yl)-1,2,4-oxadiazole

The titled compound was prepared according to the procedure of Method C using the product of Example 83D and pyrimidine-5-carboxylic acid (Maybridge). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 8.41 (dd, *J*=5.4, 2.4 Hz, 1 H), 9.44 (s, 1 H), 9.47 (dd, *J*=5.4, 1.4 Hz, 1 H), 9.59 (s, 2 H), 9.90 (dd, *J*=2.2, 1.2 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z*= 227 (M+H)<sup>+</sup>.

Example 983-(pyridazin-4-yl)-5-(2,3,6-trifluorophenyl)-1,2,4-oxadiazole

The titled compound was prepared according to the procedure of Method D using the product of Example 83D and 2,3,6-trifluorobenzoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.28 - 7.37 (m, *J*=9.5, 9.5, 3.7, 2.4 Hz, 1 H), 7.67 - 7.79 (m, *J*=9.6, 9.6, 8.7, 4.9 Hz, 1 H), 8.39 (dd, *J*=5.3, 2.2 Hz, 1 H), 9.46 (dd, *J*=5.3, 1.2 Hz, 1 H), 9.88 (dd, *J*=2.2, 1.2 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z*= 279 (M+H)<sup>+</sup>.

Example 993-(pyridazin-4-yl)-5-(2,3,4-trifluorophenyl)-1,2,4-oxadiazole

The titled compound was prepared according to the procedure of Method D using the product of Example 83D and 2,3,4-trifluorobenzoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.40 - 7.50 (m, *J*=9.3, 9.3, 7.0, 2.2 Hz, 1 H), 8.10 - 8.20 (m, 1 H), 8.39 (dd, *J*=5.4, 2.4 Hz, 1 H), 9.46 (dd, *J*=5.3, 1.2 Hz, 1 H), 9.87 (dd, *J*=2.2, 1.2 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z*= 279 (M+H)<sup>+</sup>.

Example 100*N,N*-dimethyl-*N'*-(4-(3-(pyridazin-4-yl)-1,2,4-oxadiazol-5-yl)phenylsulfonyl)formimidamide

The titled compound was prepared according to the procedure of Method D using the product of Example 83D and 4-sulfamidobenzoyl chloride dimethylformamide complex (Alfa Aesar). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 2.95 (s, 3H), 3.18 (s, 3 H), 8.06 (d, *J*=8.5 Hz, 2 H), 8.29 (s, 1 H), 8.31 (dd, *J*=5.3, 2.2 Hz, 1 H), 8.37 (d, *J*=8.8 Hz, 2 H), 9.54 (dd, *J*=5.1, 1.4 Hz, 1 H), 9.83 (dd, *J*=2.4, 1.4 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z*= 359 (M+H)<sup>+</sup>.

Example 1015-(3,4-difluorophenyl)-3-(pyrimidin-5-yl)-1,2,4-oxadiazole tosylateExample 101A5-(3,4-Difluorophenyl)-3-(pyrimidin-5-yl)-1,2,4-oxadiazole

The titled compound was prepared according to the procedure of Method D using the product of Example 79C and 3,4-difluorobenzoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.35 - 7.48 (m, 1 H), 7.97 - 8.13 (m, 2 H), 9.40 (s, 1 H), 9.49 (s, 2 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 261 (M+H)<sup>+</sup>.

Example 101B5-(3,4-Difluorophenyl)-3-(pyrimidin-5-yl)-1,2,4-oxadiazole tosylate

A solution of the product of Example 101A (52 mg, 0.2 mmol) in ethyl acetate (5 mL) was stirred with a solution of *p*-toluenesulfonic acid monohydrate (Aldrich, 46.0 mg, 0.24 mmol) in ethyl acetate (1.0 mL) at ambient temperature for 10 hours. The precipitates were collected by filtration and dried to give the title compound. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ

2.40 (s, 3 H), 7.25 (d,  $J = 8.2$  Hz, 2 H), 7.36 - 7.53 (m, 1 H), 7.83 (d,  $J = 8.3$  Hz, 2 H), 8.03-8.12 (m, 2 H), 9.57 (s, 1 H), 9.71 (s, 2 H); MS (DCI/NH<sub>3</sub>)  $m/z$  261 (M+H)<sup>+</sup>.

#### Example 102

##### 5 3-(3,4-difluorophenyl)-5-(pyrimidin-5-yl)-1,2,4-oxadiazole

The titled compound was prepared according to the procedure of Method D using 3,4-difluoro-*N*'-hydroxybenzimidamide (Tyger) and pyrimidine-5-carbonyl chloride. The pyrimidine-5-carbonyl chloride was prepared by the reaction of pyrimidine-5-carboxylic acid (Maybridge, 138 mg, 1.0 mmol) with oxalyl chloride (Aldrich, 2 M, in CH<sub>2</sub>Cl<sub>2</sub>, 1.0 mL, 2.0  
10 mmol) and a drop of dimethylformamide at room temperature over 1 hour with subsequent removal of volatiles under reduced pressure. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.72 (dt,  $J = 10.5, 8.5$  Hz, 1 H), 7.94 - 8.05 (m, 1 H), 8.11 (ddd,  $J = 10.9, 7.7, 2.0$  Hz, 1 H), 8.12 (none, 1 H), 9.51 (s, 1 H), 9.54 (s, 2 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  261 (M+H)<sup>+</sup>.

#### 15 Example 103

##### 3-(Pyrimidin-5-yl)-5-(2,3,4-trifluorophenyl)-1,2,4-oxadiazole

The titled compound was prepared according to the procedure of Method D using the product of Example 79C and 2,3,4-trifluorobenzoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.58 - 7.75 (m, 1 H), 8.03 - 8.26 (m, 1 H), 9.44 (s, 2 H), 9.45 (s, 1 H) ppm; MS  
20 (DCI/NH<sub>3</sub>)  $m/z$  279 (M+H)<sup>+</sup>, 296 (M+NH<sub>4</sub>)<sup>+</sup>.

#### Example 104

##### 3-(pyrimidin-5-yl)-5-(2,3,6-trifluorophenyl)-1,2,4-oxadiazole

The titled compound was prepared according to the procedure of Method D using the  
25 product of Example 79C and 2,3,6-trifluorobenzoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.48 - 7.61 (m, 1 H), 7.89 - 8.07 (m, 1 H), 9.44 (s, 2 H), 9.45 (s, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  279 (M+H)<sup>+</sup>, 296 (M+NH<sub>4</sub>)<sup>+</sup>.

#### Example 105

##### 30 3-(pyrimidin-5-yl)-5-(2,3,4,5-tetrafluorophenyl)-1,2,4-oxadiazole

The titled compound was prepared according to the procedure of Method D using the product of Example 79C and 2,3,4,5-tetrafluorobenzoyl chloride (Aldrich). <sup>1</sup>H NMR (300

MHz, DMSO-*d*<sub>6</sub>) δ 8.18 - 8.42 (m, 1 H), 9.45 (s, 2 H), 9.46 (s, 1 H) ppm; MS (DCI/NH<sub>3</sub>) m/z 297 (M+H)<sup>+</sup>, 314 (M+NH<sub>4</sub>)<sup>+</sup>.

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#### Example 106

##### 5-(imidazo[1,5-a]pyridin-6-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to Method C using imidazo[1,2-a]pyridine-6-carboxylic acid (Maybridge) and *N'*-hydroxynicotinimidamide (Tyger). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.67 (ddd, *J*=8.1, 4.8, 1.0 Hz, 1 H), 7.76 (d, *J*=1.4 Hz, 1 H), 7.78 - 7.92 (m, 2 H), 8.21 (s, 1 H), 8.46 (dt, *J*=8.2, 1.8 Hz, 1 H), 8.83 (dd, *J*=4.7, 1.7 Hz, 1 H), 9.27 (dd, *J*=2.2, 0.8 Hz, 1 H), 9.69 (dd, *J*=1.7, 1.0 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) m/z 264(M+H)<sup>+</sup>.

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#### Example 107

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##### 5-(1*H*-indol-6-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to Method C using 1*H*-indole-6-carboxylic acid (Aldrich) and *N'*-hydroxynicotinimidamide (Tyger). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 6.62 (ddd, *J*=3.0, 1.9, 0.8 Hz, 1 H), 7.62 - 7.71 (m, 2 H), 7.76 - 7.89 (m, 2 H), 8.27 - 8.33 (m, *J*=1.4 Hz, 1 H), 8.46 (dt, *J*=8.2, 1.9, 1.7 Hz, 1 H), 8.82 (dd, *J*=4.7, 1.7 Hz, 1 H), 9.27 (dd, *J*=2.2, 0.8 Hz, 1 H), 11.66 (s, 1 H) ppm; MS (DCI/NH<sub>3</sub>) m/z 263 (M+H)<sup>+</sup>.

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#### Example 108

##### 5-(2,7-dimethylpyrazolo[1,5-a]pyrimidin-6-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according Method C using 2,7-dimethylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid (Maybridge) and *N'*-hydroxynicotinimidamide (Tyger). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 2.52 (s, 3 H), 3.27 (s, 3 H), 6.77 (s, 1 H), 7.67 (ddd, *J*=8.0, 4.9, 0.7 Hz, 1 H), 8.48 (dt, *J*=8.6, 1.9 Hz, 1 H), 8.84 (dd, *J*=4.7, 1.7 Hz, 1 H), 9.06 (s, 1 H), 9.30 (dd, *J*=2.2, 0.8 Hz, 1 H), 9.30 (d, *J*=1.4 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) m/z 293 (M+H)<sup>+</sup>.

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Example 1095-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to Method C using 2,2-difluorobenzo[d][1,3]dioxole-5-carboxylic acid (Aldrich) and *N'*-hydroxynicotinimidamide (Tyger). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.66 (ddd, *J*=8.1, 4.8, 1.0 Hz, 1 H), 7.73 (d, *J*=8.5 Hz, 1 H), 8.14 (dd, *J*=8.5, 1.7 Hz, 1 H), 8.25 (d, *J*=1.7 Hz, 1 H), 8.44 (dt, *J*=8.2, 1.9, 1.7 Hz, 1 H), 8.82 (dd, *J*=4.7, 1.7 Hz, 1 H), 9.25 (dd, *J*=2.2, 0.8 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 304 (M+H)<sup>+</sup>.

Example 1105-(2-methylbenzofuran-5-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to Method C using 2-methylbenzofuran-5-carboxylic acid (Chembridge) and *N'*-hydroxynicotinimidamide (Tyger). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 3.33 (s, 3 H), 6.58 - 6.97 (m, 1 H), 7.66 (ddd, *J*=8.0, 4.9, 1.0 Hz, 1 H), 7.78 (d, *J*=8.5 Hz, 1 H), 8.40 - 8.55 (m, 2 H), 8.82 (dd, *J*=4.7, 1.7 Hz, 1 H), 9.27 (dd, *J*=2.2, 0.8 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 278 (M+H)<sup>+</sup>.

Example 1115-(benzo[d][1,2,3]thiadiazol-5-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to Method C using benzo[d][1,2,3]thiadiazole-5-carboxylic acid (Maybridge) and *N'*-hydroxynicotinimidamide (Tyger). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.69 (ddd, *J*=8.0, 4.9, 0.7 Hz, 1 H), 8.51 (dt, *J*=8.2, 1.9, 1.7 Hz, 1 H), 8.57 (dd, *J*=8.5, 1.7 Hz, 1 H), 8.73 (d, *J*=7.8 Hz, 1 H), 8.85 (dd, *J*=4.9, 1.5 Hz, 1 H), 9.32 (dd, *J*=2.4, 1.0 Hz, 1 H), 9.51 (dd, *J*=1.7, 0.7 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 282 (M+H)<sup>+</sup>.

Example 1125-(1*H*-benzo[d]imidazol-5-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to Method C using 1*H*-benzo[d]imidazole-5-carboxylic acid (Aldrich) and *N'*-hydroxynicotinimidamide (Tyger). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.66 (ddd, *J*=8.1, 4.8, 1.0 Hz, 1 H), 7.75 - 7.98 (m, 1 H), 7.99 - 8.17 (m, 1 H), 8.34 - 8.56 (m, 3 H), 8.82 (dd, *J*=5.1, 1.7 Hz, 1 H), 9.28 (dd, *J*=2.2, 0.8 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 264 (M+H)<sup>+</sup>.

Example 1135-(1*H*-benzo[d][1,2,3]triazol-5-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to Method C using 1*H*-benzo[d][1,2,3]triazole-5-carboxylic acid (Aldrich) and *N'*-hydroxynicotinimidamide (Tyger).

5 <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.67 (ddd, *J*=8.0, 4.9, 0.7 Hz, 1 H), 8.10 - 8.20 (m, 1 H), 8.22 - 8.31 (m, 1 H), 8.49 (dt, *J*=8.1, 2.0, 1.7 Hz, 1 H), 8.75 - 8.92 (m, 2 H), 9.30 (dd, *J*=2.2, 0.8 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 265 (M+H)<sup>+</sup>.

Example 1145-(benzo[d]thiazol-5-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to Method C using benzo[d]thiazole-5-carboxylic acid (Apollo) and *N'*-hydroxynicotinimidamide (Tyger). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.64 - 7.73 (m, 1 H), 8.35 (s, 1 H), 8.36 (s, 1 H), 8.48 (dt, *J*=8.1, 2.0, 1.7 Hz, 1 H), 8.83 (dd, *J*=4.7, 1.7 Hz, 1 H), 9.17 (t, *J*=1.2 Hz, 1 H), 9.29 (dd, *J*=2.2, 0.8 Hz, 1 H), 9.66 (s, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 281 (M+H)<sup>+</sup>.

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Example 1153-(pyridin-3-yl)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1,2,4-oxadiazole

The title compound was prepared according to Method C using 1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylic acid (Adesis) and *N'*-hydroxynicotinimidamide (Tyger). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 6.71 (d, *J*=3.4 Hz, 1 H), 7.66 (ddd, *J*=7.9, 4.8, 0.8 Hz, 1 H), 7.70 (d, *J*=3.4 Hz, 1 H), 8.47 (dt, *J*=8.1, 1.9 Hz, 1 H), 8.78 - 8.86 (m, 2 H), 9.05 (d, *J*=2.0 Hz, 1 H), 9.28 (dd, *J*=2.2, 0.8 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 264 (M+H)<sup>+</sup>.

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Example 1165-(1*H*-indol-5-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to Method C using 1*H*-indole-5-carboxylic acid (Aldrich) and *N'*-hydroxynicotinimidamide (Tyger). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 6.69 (dt, *J*=2.3, 1.4 Hz, 1 H), 7.55 (t, *J*=2.7 Hz, 1 H), 7.62 - 7.70 (m, 2 H), 7.94 (dd, *J*=8.8, 1.7 Hz, 1 H), 8.46 (dt, *J*=8.1, 1.9 Hz, 1 H), 8.49 - 8.52 (m, 1 H), 8.81 (dd, *J*=4.7, 1.7 Hz, 1 H), 9.27 (dd, *J*=2.2, 0.8 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 263 (M+H)<sup>+</sup>.

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Example 1175-(benzofuran-5-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to Method C using benzofuran-5-carboxylic acid (Aldrich) and *N'*-hydroxynicotinimidamide (Tyger). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.20 (dd, *J*=2.0, 1.0 Hz, 1 H), 7.66 (ddd, *J*=7.9, 4.8, 0.8 Hz, 1 H), 7.91 (dt, *J*=8.6, 1.0, 0.8 Hz, 1 H), 8.14 - 8.24 (m, 2 H), 8.47 (dt, *J*=7.9, 2.0 Hz, 1 H), 8.60 (d, *J*=1.4 Hz, 1 H), 8.82 (dd, *J*=4.7, 1.7 Hz, 1 H), 9.28 (dd, *J*=2.2, 0.8 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 264 (M+H)<sup>+</sup>.

Example 1185-(1-methyl-1H-benzo[d]imidazol-5-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to Method C using 1-methyl-1H-benzo[d]imidazole-5-carboxylic acid (Maybridge) and *N'*-hydroxynicotinimidamide (Tyger). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.65 (ddd, *J*=8.0, 4.9, 0.7 Hz, 1 H), 7.68 - 7.88 (m, *J*=8.8 Hz, 1 H), 7.87 - 8.10 (m, 2 H), 8.14 - 8.37 (m, 1 H), 8.46 (dt, *J*=8.1, 1.9 Hz, 1 H), 8.82 (dd, *J*=4.7, 1.7 Hz, 1 H), 9.27 (dd, *J*=2.0, 0.7 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 278 (M+H)<sup>+</sup>.

Example 1193-(imidazo[1,2-a]pyridin-6-yl)-5-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to Method D using *N'*-hydroxyimidazo[1,2-a]pyridine-6-carboximidamide (Bionet) and nicotinoyl chloride, hydrochloric Acid (Aldrich). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.62 - 7.91 (m, 4 H), 8.20 (s, 1 H), 8.56 (dt, *J*=8.1, 1.9 Hz, 1 H), 8.92 (dd, *J*=4.7, 1.7 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 264 (M+H)<sup>+</sup>.

Example 1205-(6-chloropyridin-3-yl)-3-(imidazo[1,2-a]pyridin-6-yl)-1,2,4-oxadiazole

The title compound was prepared according to Method D using *N'*-hydroxyimidazo[1,2-a]pyridine-6-carboximidamide (Bionet) and 6-chloronicotinoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.70 (d, *J*=1.2 Hz, 1 H), 7.74 - 7.84 (m, 2 H), 7.87 (d, *J*=8.3 Hz, 1 H), 8.20 (s, 1 H), 8.59 (dd, *J*=8.5, 2.6 Hz, 1 H), 9.20 (dd, *J*=2.4, 0.8 Hz, 1 H), 9.47 (t, *J*=1.4 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 298 (M+H)<sup>+</sup>, 300 (M+H)<sup>+</sup>.

Example 1215-(6-fluoropyridin-3-yl)-3-(imidazo[1,2-a]pyridin-6-yl)-1,2,4-oxadiazole

The title compound was prepared according to Method C using *N'*-hydroxyimidazo[1,2-a]pyridine-6-carboximidamide (Bionet) and 6-fluoronicotinic acid (Frontier). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.55 (ddd, *J*=8.5, 2.7, 0.7 Hz, 1 H), 7.70 (d, *J*=1.4 Hz, 1 H), 7.73 - 7.86 (m, 2 H), 8.20 (s, 1 H), 8.75 (ddd, *J*=8.1, 2.5 Hz, 1 H), 9.08 (dt, *J*=1.7, 0.8 Hz, 1 H), 9.46 (dd, *J*=1.7, 1.0 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 282 (M+H)<sup>+</sup>.

Example 1225-(5-fluoropyridin-3-yl)-3-(imidazo[1,2-a]pyridin-6-yl)-1,2,4-oxadiazole

The title compound was prepared according to method C using *N'*-hydroxyimidazo[1,2-a]pyridine-6-carboximidamide (Bionet) and 5-fluoronicotinic acid (Frontier). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.71 (d, *J*=1.4 Hz, 1 H), 7.74 - 7.88 (m, 2 H), 8.20 (s, 1 H), 8.51 (ddd, *J*=9.0, 2.9, 1.7 Hz, 1 H), 8.97 (d, *J*=3.1 Hz, 1 H), 9.24 (t, *J*=1.5 Hz, 1 H), 9.47 (t, *J*=1.4 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 282 (M+H)<sup>+</sup>.

Example 1235-(1*H*-indazol-5-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to Method C using 1*H*-indazole-5-carboxylic acid (ABCR) and *N'*-hydroxynicotinimidamide (Tyger). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.7 (dd, *J*=7.9, 4.8 Hz, 1 H), 7.8 (d, *J*=8.7 Hz, 1 H), 8.2 (dd, *J*=8.7, 1.6 Hz, 1 H), 8.4 (s, 1 H), 8.5 (dt, *J*=7.9, 1.8 Hz, 1 H), 8.7 (s, 1 H), 8.8 (dd, *J*=4.8, 1.6 Hz, 1 H), 9.3 (d, *J*=2.0 Hz, 1 H), 13.6 (s, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 264 (M+H)<sup>+</sup>.

Example 1245-([1,2,4]triazolo[4,3-*a*]pyridin-6-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazoleExample 124A5-(6-Chloropyridin-3-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to Method D using *N'*-hydroxynicotinimidamide (Tyger) and 6-chloronicotinoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.48 (dd, *J*=7.6, 5.3 Hz, 1 H), 7.57 (d, *J*=8.5 Hz, 1 H), 8.40 - 8.48 (m, 2 H),

8.80 (dd,  $J=4.7, 1.7$  Hz, 1 H), 9.24 (d,  $J=2.4$  Hz, 1 H), 9.40 (d,  $J=2.4$  Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  259 (M+H)<sup>+</sup>, 261 (M+H)<sup>+</sup>.

#### Example 124B

##### 5 5-(6-Hydrazinylpyridin-3-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

A suspension of the product of Example 126A (260 mg, 1 mmol) in EtOH (15 mL) was stirred with hydrazine (Aldrich, 50 mg, 2.5 mmol) at refluxing temperature for 2 h and then cooled to room temperature. The precipitates were collected by filtration, washed with addition cooled EtOH (5 mL) and dried to give the title compound. <sup>1</sup>NMR (DMSO-*d*<sub>6</sub>):  $\delta$  6.77 - 7.08 (m, 1 H), 7.35 - 7.44 (m, 2 H), 7.63 (ddd,  $J=8.0, 4.9, 1.0$  Hz, 1 H), 7.79 (tt,  $J=7.6, 1.9$  Hz, 1 H), 8.12 (dd,  $J=8.8, 2.4$  Hz, 1 H), 8.41 (dt,  $J=8.1, 1.9$  Hz, 1 H), 8.58 (dt,  $J=4.0, 1.9$  Hz, 1 H), 8.75 - 8.84 (m, 1 H), 9.22 (dd,  $J=2.2, 0.8$  Hz, 1 H) ppm, MS (DCI/NH<sub>3</sub>)  $m/z=$  255 (M+H)<sup>+</sup>.

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#### Example 124C

##### 5-([1,2,4]triazolo[4,3-a]pyridin-6-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

A suspension of the product of Example 126B (80 mg, 0.31 mmol) in triethoxymethane (Aldrich, 4 mL) was heated to reflux for 16 hours. The reaction mixture was cooled to room temperature and the volatiles were removed under vacuum. The residue was purified with chromatography (SiO<sub>2</sub>, EtOAc/CH<sub>2</sub>Cl<sub>2</sub> = 1/9) to give the title compound. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  7.68 (dd,  $J=8.1, 5.0$  Hz, 1 H), 7.90 - 8.11 (m, 2 H), 8.46 (dt,  $J=7.9, 2.0$  Hz, 1 H), 8.84 (dd,  $J=4.8, 1.6$  Hz, 1 H), 9.27 (d,  $J=2.0$  Hz, 1 H), 9.44 (s, 1 H), 9.68 (s, 1 H) ppm; MS (DCI/NH<sub>3</sub>)  $m/z=$  265 (M+H)<sup>+</sup>.

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#### Example 125

##### 5-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzo[d]oxazol-2(3*H*)-one

The title compound was prepared according to Method C using 2-oxo-2,3-dihydrobenzo[d]oxazole-5-carboxylic acid (Matrix) and *N*<sup>1</sup>-hydroxynicotinimidamide (Tyger). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  7.40 (d,  $J=8.5$  Hz, 1 H), 7.64 (ddd,  $J=8.0, 5.0, 0.9$  Hz, 1 H), 7.90 (d,  $J=1.7$  Hz, 1 H), 8.01 (dd,  $J=8.3, 1.9$  Hz, 1 H), 8.55 (dt,  $J=7.8, 1.9$  Hz, 1 H), 8.74 (dd,  $J=4.8, 1.7$  Hz, 1 H), 9.29 (dd,  $J=2.2, 0.9$  Hz, 1 H). ppm; MS (DCI/NH<sub>3</sub>)  $m/z$  281 (M+H)<sup>+</sup>.

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Example 1265-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)-1H-benzo[d]imidazole-2(3H)-thione

The title compound was prepared according to Method C using 2-mercapto-5-benzimidazolecarboxylic acid (Princeton) and *N'*-hydroxynicotinimidamide (Tyger). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.38 (d, *J*=8.5 Hz, 1 H), 7.65 (ddd, *J*=8.0, 4.9, 0.7 Hz, 1 H), 7.86 (d, *J*=1.0 Hz, 1 H), 8.00 (dd, *J*=8.1, 1.7 Hz, 1 H), 8.45 (dt, *J*=8.0, 1.9 Hz, 1 H), 8.81 (dd, *J*=4.9, 1.5 Hz, 1 H), 9.26 (dd, *J*=2.2, 0.9 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 296 (M+H)<sup>+</sup>.

Example 1271,3-dimethyl-5-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)-1H-benzo[d]imidazol-2(3H)-one

The title compound was prepared according to Method C using 1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (Matrix) and *N'*-hydroxynicotinimidamide (Tyger). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 3.49 (s, 3 H), 3.53 (s, 3 H), 7.36 (d, *J*=8.3 Hz, 1 H), 7.64 (ddd, *J*=8.0, 5.1, 0.8 Hz, 1 H), 7.98 (d, *J*=1.6 Hz, 1 H), 8.08 (dd, *J*=8.3, 1.6 Hz, 1 H), 8.55 (dt, *J*=8.0, 1.9 Hz, 1 H), 8.73 (dd, *J*=4.8, 1.6 Hz, 1 H) 9.29 (d, *J*=1.2 Hz, 1 H). MS (DCI/NH<sub>3</sub>) *m/z* 308 (M+H)<sup>+</sup>.

Example 1286-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzo[d]oxazol-2(3H)-one

The title compound was prepared according to Method C using 2-oxo-2,3-dihydrobenzo[d]oxazole-6-carboxylic acid (Eur. J. Med. Chem. 1974, 9, 491-6.) and *N'*-hydroxynicotinimidamide (Tyger). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.35 (d, *J*=8.7 Hz, 1 H), 7.65 (dd, *J*=7.5, 4.4 Hz, 1 H), 8.04 (d, *J*=1.6 Hz, 1 H), 8.07 (s, 1 H), 8.44 (dt, *J*=7.9, 2.0 Hz, 1 H), 8.82 (dd, *J*=4.8, 1.6 Hz, 1 H), 9.25 (d, *J*=1.6 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 281 (M+H)<sup>+</sup>.

Example 1295-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)-1H-benzo[d]imidazol-2(3H)-one trifluoroacetic Acid

A solution of 2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxylic acid (Princeton, 178 mg, 1.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (anhydrous, 5.0 mL) was stirred with oxalyl chloride (Aldrich, 2 M, in CH<sub>2</sub>Cl<sub>2</sub>, 1.0 mL) in the presence of 2 drops dimethylformamide at room temperature for 1 hour. It was then concentrated and dried under reduced pressure. The residue was

dissolved in pyridine (5.00 mL) and then stirred with *N'*-hydroxynicotinimidamide (Tyger, 137 mg, 1.0 mmol) at 100 °C for 16 hours. The reaction mixture was cooled to ambient temperature, diluted with EtOAc (50 mL), washed with water (2 x 10 mL) and brine. The organic solution was concentrated under reduced pressure, purified with preparative HPLC  
5 [Waters, column: Xbridge™ Prep C18 5μm, OBD™ 30 x 100 mm, solvent: acetonitrile/water(v.1% TFA), 5/95 to 95/5, flow rate of 40 mL/minute. Fractions were collected based upon UV signal threshold.] the title compound. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.25 (d, *J*=8.3 Hz, 1 H), 7.75 (ddd, *J*=7.9, 5.2, 0.8 Hz, 1 H), 7.88 (d, *J*=1.6 Hz, 1 H), 7.99 (dd, *J*=8.3, 1.6 Hz, 1 H), 8.68 (dt, *J*=7.9, 1.8 Hz, 1 H), 8.79 (dd, *J*=5.2, 1.6 Hz, 1 H), 9.33 (d,  
10 *J*=1.2 Hz, 1 H) ppm. MS (DCI/NH<sub>3</sub>) *m/z* 280 (M+H)<sup>+</sup>.

#### Example 130

#### 6-(3-(Pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzo[d]oxazol-2-amine

#### Example 130A

#### 2-nitro-5-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenol

The title compound was prepared according to Method C using 3-hydroxy-4-nitrobenzoic acid (Aldrich) and *N'*-hydroxynicotinimidamide (Tyger). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.67 (ddd, *J*=7.9, 4.8, 0.8 Hz, 1 H), 7.76 (dd, *J*=8.5, 1.8 Hz, 1 H), 7.92 (d, *J*=1.6  
20 Hz, 1 H), 8.12 (d, *J*=8.3 Hz, 1 H), 8.45 (dt, *J*=7.9, 2.0 Hz, 1 H), 8.83 (dd, *J*=4.8, 1.6 Hz, 1 H), 9.26 (d, *J*=1.2 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 285 (M+H)<sup>+</sup>.

#### Example 130B

#### 2-amino-5-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)phenol

A solution of the product of Example 132A (1.0 g, 3.52 mmol) in THF (20 .0 mL) was stirred with Raney nickel (Aldrich, 4.0 g) under H<sub>2</sub> (30 psi) for 2 hours. The catalyst was then carefully removed by filtration and the reaction mixture was concentrated to give the title compound. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 5.67 (s, 2 H), 6.74 (d, *J*=8.1 Hz, 1 H), 7.40 - 7.52 (m, 2 H), 7.62 (dd, *J*=8.0, 4.2 Hz, 1 H), 8.39 (dt, *J*=8.0, 2.0, 1.9 Hz, 1 H), 8.78 (dd,  
30 *J*=4.7, 1.7 Hz, 1 H), 9.20 (d, *J*=1.7 Hz, 1 H), 9.65 - 9.98 (m, *J*=3.4 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 255 (M+H)<sup>+</sup>.

Example 130C6-(3-(Pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzo[d]oxazol-2-amine

To a solution of the product of Example 132B (254 mg, 1.0 mmol) in THF (20 ml) was added cyanic bromide (Aldrich, 106 mg, 1.0 mmol) and triethylamine (Aldrich, 0.14 ml, 1.0 mmol). The mixture was then stirred at 50 °C for 10 h, cooled to ambient temperature, trituated with water (40 mL). The precipitate was filtered and dried under vacuum to give the titled compound. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.42 (d, *J*=8.1 Hz, 1 H), 7.65 (dd, *J*=7.8, 5.1 Hz, 1 H), 7.98 (s, 2 H), 8.02 (dd, *J*=8.1, 1.7 Hz, 1 H), 8.12 (d, *J*=1.7 Hz, 1 H), 8.44 (dt, *J*=8.1, 1.9 Hz, 1 H), 8.81 (dd, *J*=4.7, 1.7 Hz, 1 H), 9.26 (d, *J*=1.4 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 280 (M+H)<sup>+</sup>.

Example 1316-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzo[d]oxazole

To a solution of the product of Example 132B (508 mg, 2.0 mmol) in triethyl orthoformate (Aldrich, 20 mL, 120 mmol) was stirred at 100 °C for 10 hours. It was then cooled to ambient temperature, and then trituated with hexanes (50 mL). The precipitate was filtered and dried under vacuum to give the titled compound. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.67 (ddd, *J*=7.9, 4.8, 0.8 Hz, 1 H), 8.10 (d, *J*=8.3 Hz, 1 H), 8.28 (dd, *J*=8.3, 1.6 Hz, 1 H), 8.48 (dt, *J*=7.9, 2.0 Hz, 1 H), 8.66 (d, *J*=1.6 Hz, 1 H), 8.83 (dd, *J*=4.8, 1.6 Hz, 1 H), 9.04 (s, 1 H), 9.29 (d, *J*=2.4 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 265 (M+H)<sup>+</sup>.

Example 1325-(5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzo[d]oxazol-2(3*H*)-oneExample 132A2-oxo-2,3-dihydrobenzo[d]oxazole-5-carbonitrile

A solution of 3-Amino-4-hydroxybenzonitrile (Betapharma, 537 mg, 4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 ml) was stirred with *N,N'*-carbonyldiimidazole (Aldrich, 713 mg, 4.40 mmol) at room temperature for 16 hours. It was then concentrated under reduced pressure. The residue was stirred with water (10 mL) for 5 minutes, and extracted with EtOAc (3 x 10 mL). The combined extracts were concentrated to the title compound. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.17 - 7.22 (m, 1 H), 7.28 - 7.34 (m, 2 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 178 (M+NH<sub>4</sub>)<sup>+</sup>.

Example 132B*N'*-Hydroxy-2-oxo-2,3-dihydrobenzo[d]oxazole-5-carboximidamide

A solution of the product from Example 134A (300 mg, 1.9 mmol), hydroxylammonium chloride (Aldrich, 64.0 mg, 1.9 mmol) and triethylamine (Aldrich, 227 mg, 2.3 mmol), in methanol (10 mL) was stirred at 65 °C for 2 h, cooled to ambient temperature, then concentrated under reduced pressure. The residue was triturated with EtOAc (10 mL). The precipitate was filtered and dried under vacuum to give the titled compound. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.22 (d, *J*=8.33 Hz, 1 H) 7.34-7.43 (m, 2 H). MS (DCI/NH<sub>3</sub>) *m/z* 194 (M+H)<sup>+</sup>.

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Example 132C5-(5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzo[d]oxazol-2(3H)-one

The title compound was prepared according to Method D using the product of Example 134B and nicotinoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.51 (d, *J*=8.7 Hz, 1 H), 7.68 - 7.75 (m, 2 H), 7.87 (dd, *J*=8.3, 2.0 Hz, 1 H), 8.57 (dt, *J*=7.9, 2.0 Hz, 1 H), 8.90 (dd, *J*=5.0, 1.8 Hz, 1 H), 9.36 (d, *J*=1.6 Hz, 1 H) ppm. MS (DCI/NH<sub>3</sub>) *m/z* 281 (M+H)<sup>+</sup>.

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Example 1335-(5-(6-chloropyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzo[d]oxazol-2(3H)-one

The title compound was prepared according to Method D using the product of Example 134B and 6-chloronicotinoyl chloride (Aldrich). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.33 (d, *J*=8.3 Hz, 1 H), 7.73 (dd, *J*=8.3, 0.8 Hz, 1 H), 7.82 (d, *J*=1.6 Hz, 1 H), 7.91 (dd, *J*=8.3, 1.6 Hz, 1 H), 8.57 (dd, *J*=8.3, 2.4 Hz, 1 H), 9.19 (d, *J*=2.4 Hz, 1 H) ppm. MS (DCI/NH<sub>3</sub>) *m/z* 315 317 (M+H)<sup>+</sup>.

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Example 1345-(benzo[d][1,3]dioxol-5-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole

The title compound was prepared according to method C using benzo[d][1,3]dioxole-5-carboxylic acid (Aldrich) and *N'*-hydroxynicotinimidamide (Tyger). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 6.22 (s, 2 H), 7.20 (d, *J*=8.1 Hz, 1 H), 7.61 - 7.69 (m, 2 H), 7.81 (dd, *J*=8.1, 1.7 Hz, 1 H), 8.42 (dt, *J*=8.2, 1.9, 1.7 Hz, 1 H), 8.81 (dd, *J*=4.7, 1.7 Hz, 1 H), 9.24 (dd, *J*=2.2, 0.8 Hz, 1 H) ppm; MS (DCI/NH<sub>3</sub>) *m/z* 268 (M+H)<sup>+</sup>.

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In addition to the specific compounds, one of ordinary skill in the art would readily recognize that a variety of pharmaceutically acceptable salts, esters, amides, and prodrugs of a parent compound also could be incorporated into a composition, method, or article of manufacture of the present invention.

Suitable pharmaceutically acceptable basic addition salts include, but are not limited to cations based on alkali metals or alkaline earth metals such as lithium, sodium, potassium, calcium, magnesium and aluminum salts and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine and the like. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanalamine, diethanolamine, piperidine, piperazine and the like.

Other possible compounds include pharmaceutically acceptable amides and esters. For a description of pharmaceutically acceptable esters as prodrugs, see Bundgaard, E., ed., (1985) *Design of Prodrugs*, Elsevier Science Publishers, Amsterdam, which is hereby incorporated by reference. These esters are typically formed from the corresponding carboxylic acid and an alcohol. Generally, ester formation can be accomplished via conventional synthetic techniques. (See, e.g., *March Advanced Organic Chemistry*, 3rd Ed., John Wiley & Sons, New York p. 1157 (1985) and references cited therein, and Mark et al. *Encyclopedia of Chemical Technology*, John Wiley & Sons, New York (1980), both of which are hereby incorporated by reference. The alcohol component of the ester will generally comprise (i) a C<sub>2</sub>-C<sub>12</sub> aliphatic alcohol that can or can not contain one or more double bonds and can or can not contain branched carbons or (ii) a C<sub>7</sub>-C<sub>12</sub> aromatic or heteroaromatic alcohols. This invention also contemplates the use of those compositions, which are both esters as described herein, and at the same time are the pharmaceutically acceptable salts thereof.

For a description of pharmaceutically acceptable amides as prodrugs, see Bundgaard, H., Ed., (1985) *Design of Prodrugs*, Elsevier Science Publishers, Amsterdam. These amides are typically formed from the corresponding carboxylic acid and an amine. Generally, amide formation can be accomplished via conventional synthetic techniques. (See, e.g., *Advanced Organic Chemistry*, 3rd Ed., John Wiley & Sons, New York, p. 1152 (1985) and Mark et al. *Encyclopedia of Chemical Technology*, John Wiley & Sons, New York (1980), both of which are hereby incorporated by reference. This invention also contemplates the use of those

compositions, which are amides, as described herein, and at the same time are the pharmaceutically acceptable salts thereof.

It also will be readily apparent to one with skill in the art that the compounds can be generated in vivo by administration of a drug precursor which, following administration, releases the drug in vivo via a chemical or physiological process (e.g., a parent compound on being brought to the physiological pH or through enzyme action is converted to the desired drug form).

#### Administration

As noted above, it has been discovered that pain can be treated by concurrently administering to a patient (e.g., a mammal, such as a human) in need thereof, an  $\alpha 4\beta 2$  PAM and an  $\alpha 4\beta 2$  receptor ligand. Such combination may be especially useful in expanding the dosage range for obtaining therapeutically beneficial effects.

The dosage range at which the  $\alpha 4\beta 2$  PAM and an  $\alpha 4\beta 2$  receptor ligand will be administered concurrently can vary widely. The specific dosage will be chosen by the patient's physician taking into account the particular compounds chosen, the severity of the patient's illness, any other medical conditions or diseases the patient is suffering from, other drugs the patient is taking and their potential to cause an interaction or adverse event, the patient's previous response to medication, and other factors. Suitable dosage ranges for the  $\alpha 4\beta 2$  PAM are from about 0.0001 mg/kg to 100 mg/kg of body weight. Suitable dosage ranges for the  $\alpha 4\beta 2$  receptor ligand are from about 0.0001 mg/kg to 100 mg/kg of body weight.

The  $\alpha 4\beta 2$  PAM and an  $\alpha 4\beta 2$  receptor ligand should be administered concurrently in amounts that are effective to treat the patient's pain, cognitive disorder, or related condition. In more general terms, one would create a combination of the present invention by choosing a dosage of an  $\alpha 4\beta 2$  PAM and an  $\alpha 4\beta 2$  receptor ligand according to the spirit of the guidelines presented above.

The invention also is carried out by administering an  $\alpha 4\beta 2$  PAM together with an  $\alpha 4\beta 2$  receptor ligand in any manner which provides effective levels of the compounds in the body at the same time. Typically, the combination will be administered orally.

However, the invention is not limited to oral administration. The invention should be construed to cover any route of administration that is appropriate for the medications involved and for the patient. For example, transdermal administration may be very desirable

for patients who are forgetful or petulant about taking oral medicine. Injections may be appropriate for patients refusing their medication. One of the drugs may be administered by one route, such as oral, and the others may be administered by the transdermal, percutaneous, intravenous, intramuscular, intranasal, or intrarectal route, in particular circumstances. The route of administration may be varied in any way, limited by the physical properties of the drugs and the convenience of the patient and the caregiver.

Based on the diversity of the mechanisms underlying chronic pain (e.g. nociceptive or neuropathic, degrees of pain intensity, various etiologies etc), currently available pain medications are not efficacious in all patients or in all pain conditions. Analgesics can be broadly categorized as non-opioid analgesics (acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs)), opioid analgesics (morphine) and adjuvant analgesics or co-analgesics (antiepileptic drugs and antidepressants). In a simplified classification, non-opioid analgesics are mostly used to relieve mild to moderate nociceptive pain, adjuvant analgesics (gabapentin, pregabalin) are used to relieve neuropathic pain, and opioid analgesics are used to treat severe pain of all origins, depending on the dose prescribed.

Nicotinic acetylcholine receptor ligands act at multiple locations throughout the pain pathway to relieve pain. Nicotinic acetylcholine receptor ligands are found on primary sensory neurons (periphery) where nociceptive information is initiated, in the cell body regions of these neurons (i.e. the dorsal root ganglion or DRG), the dorsal spinal cord where the first pain synapse is located, in the brainstem cell body regions that control descending innervation, as well as in the higher brain regions that integrate and perceive sensory information such as the thalamus and the cortex. The current theory supported by evidence from multiple sources (reviewed in Decker et al., Curr Topics Med Chem, 4: 369, 2004) is that anti-nociceptive effects of nAChR ligands are mediated by activation of brain stem nuclei with descending inhibitory inputs to the spinal cord. Additional pathways may also mediate analgesic effects of nAChR agonists in persistent or neuropathic pain.

Another aspect of the invention is the potential to enhance efficacy of other medications used for treating pain when combined with an  $\alpha 4\beta 2$  PAM. As noted above, examples of currently used drugs include opioids, gabapentin, pregabalin, duloxetine and others. Novel mechanisms such as cannabinoids agonists, vanilloid receptor antagonists, calcium channel blockers, potassium channel antagonists, nerve growth factor antagonists and sodium channel blockers are also being developed for the treatment of pain. For many of these mechanisms, it is emerging that a component of efficacy may be driven by activation of

5 descending inhibitory inputs. For example, opioid analgesics can block pain transmission, in part by increasing descending inhibitory pathways to modulate pain transmission at the spinal level (Pasternack, G.W., Clin Neuropaharmacol. 16: 1, 1993; Lauretti, G.T., Expert Reviews in Neurotherapeutics, 6: 613-622. 2006). Since these drugs exert their effect via activating  
5 descending inhibitory inputs, and these pathways can be shared or commonly activated by  $\alpha 4\beta 2$  nAChR ligands, it is anticipated that co-administration of  $\alpha 4\beta 2$  selective PAMs can lead to enhanced efficacy of other analgesic agents by amplifying the descending inhibitory control of spinal cord activation. Thus, combination with  $\alpha 4\beta 2$  PAMs enables the opportunity to create analgesic medications with either a broader or superior spectrum of  
10 efficacy that would improve the treatment of chronic pain.

Other nAChR-mediated diseases or disorders also can benefit from such concurrent administration. The combination of  $\alpha 4\beta 2$  nAChR ligands and  $\alpha 4\beta 2$  selective PAMs can be used for treatment of diseases or disorders related to the cholinergic system of the central nervous system, the peripheral nervous system, diseases or disorders related to smooth  
15 muscle contraction, endocrine diseases or disorders, diseases or disorders related to neurodegeneration, diseases or disorders related to inflammation, and withdrawal symptoms caused by the termination of abuse of chemical substances, in for example nicotine, as well as pain. In a particular embodiment, the combination is useful for conditions and disorders related to attention deficit disorder, attention deficit hyperactivity disorder (ADHD), Alzheimer's  
20 disease (AD), schizophrenia, mild cognitive impairment, age-associated memory impairment (AAMI), senile dementia, AIDS dementia, Pick's Disease, dementia associated with Lewy bodies, dementia associated with Down's syndrome, schizophrenia, smoking cessation, substance abuse, amyotrophic lateral sclerosis, Huntington's disease, diminished CNS function associated with traumatic brain injury, acute pain, post-surgical pain, chronic pain,  
25 inflammatory pain, neuropathic pain, infertility, lack of circulation, need for new blood vessel growth associated with wound healing, more particularly circulation around a vascular occlusion, need for new blood vessel growth associated with vascularization of skin grafts, ischemia, inflammation, sepsis, wound healing, and other complications associated with diabetes, among other systemic and neuroimmunomodulatory activities. The method is  
30 useful for conditions and disorders related to conditions and disorders characterized by neuropsychological and cognitive dysfunction, for example in Alzheimer's disease, bipolar disorder, schizophrenia, schizoaffective disorder, and other related disorders characterized by neuropsychological and cognitive dysfunction, in particular.

For example, one embodiment relates to a method of use for treating or preventing a condition or disorder characterized by attention or cognitive dysfunction, such as Alzheimer's disease and ADHD, among other condition and disorders. The method comprises the step of administering a therapeutically effective amount of a nicotinic acetylcholine receptor subtype  $\alpha 4\beta 2$  positive allosteric modulator to a subject in need thereof in combination with a drug that improves cholinergic function. Examples of such drugs are nicotinic acetylcholine receptor ligands and acetylcholinesterase inhibitors.

Another method of use relates to treating or preventing a condition or disorder characterized by neuropsychological dysfunction, for example schizophrenia, wherein the method comprises the step of administering a therapeutically effective amount of a nicotinic acetylcholine receptor subtype  $\alpha 4\beta 2$  positive allosteric modulator to a subject in need thereof in combination with an antipsychotic agent.

#### BIOLOGICAL ACTIVITY

Example A:  $\alpha 4\beta 2$  Positive allosteric modulator enhances the effects of nicotinic agonists.

#### Calcium Flux Assays using Cells Expressing nAChR Subtypes

*Experimental Procedure:* Human embryonic kidney (HEK) 293 cells stably expressing human  $\alpha 4\beta 2$  or  $\alpha 3\beta 4$  combinations are grown to confluency in 162 cm<sup>2</sup> tissue culture flasks in DMEM media supplemented with 10% FBS and 25  $\mu$ g/ml zeocin and 200  $\mu$ g/ml hygromycin B. IMR-32 neuroblastoma cells (ATCC) are grown to confluency in 162 cm<sup>2</sup> tissue culture flasks in minimum essential media supplemented with 10% FBS and 1 mM sodium pyruvate, 1 % non-essential amino acids and 1% antibiotic-antimycotic. The cells are then dissociated using cell dissociation buffer and 100-150  $\mu$ l per well of  $3.5 \times 10^5$  cells/ml cell suspension (~50,000 –100,000 cells/well) was plated into 96-well black plates (poly-D-lysine precoated) with clear bottom and maintained for 24-48 hours in a tissue culture incubator at 37 °C under an atmosphere of 5% CO<sub>2</sub>: 95% air. Other clonal cell lines or primary cell cultures that express endogenous  $\alpha 4^*$  nicotinic receptors may also be used in this assay. Calcium flux was measured using calcium-3 assay kit (Molecular Devices, Sunnyvale, CA) or fluo-4 (Invitrogen). A stock solution of the dye was prepared by dissolving each vial supplied by the vendor in Hank's balanced salt solution buffer (HBSS) or 150 mM NMDG, 20 mM CaCl<sub>2</sub> containing 10 mM HEPES, The stock solution was diluted

1:20 using the same buffer before use. The growth media was removed from the cells. The cells were loaded with 100  $\mu$ l of the dye per well and incubated at room temperature for up to one hour for HEK 293 clonal stable cell lines or 30 minutes – 45 minutes at 37 °C for IMR-32 cells. Fluorescence measurements were read simultaneously from all the wells by a  
5 Fluorometric Imaging Plate Reader (FLIPR) at an excitation wavelength of 480 nm and an emission wavelength of 520 nm. Baseline fluorescence was measured for the first 6 seconds at which 3X concentrations of modulator/test compounds were added to the cell plate at 50  $\mu$ l and incubated for five minutes. The fluorescence intensity was captured every second for the first 1 minute followed by every 5 seconds for an additional 4 minutes. This procedure was  
10 followed by 50  $\mu$ l of 4X concentration of agonist and readings were taken for a period of 3-5 minutes as described above. Data was normalized to maximal responses and plotted as a function of concentration. The concentration dependence of changes fluorescence responses was fitted by nonlinear regression analysis (GraphPad Prism, San Diego, CA) to obtain EC<sub>50</sub> values.

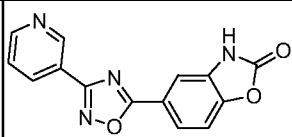
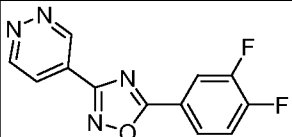
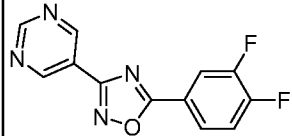
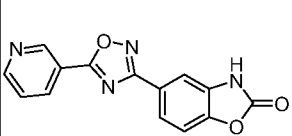
15 The positive allosteric modulator effects on  $\alpha$ 4 $\beta$ 2nAChRs exemplified by 3-(3-pyridin-3-yl-1,2,4-oxadiazol-5-yl)benzotrile (Compound 1) and 3,5-di(pyridin-3-yl)-1,2,4-oxadiazole (Compound 2) can be identified by measuring their potentiating effect to fluorescence changes in intracellular calcium using a fluorimetric plate reader. The potentiating effect of an  $\alpha$ 4 $\beta$ 2modulator on  $\alpha$ 4 $\beta$ 2receptor can also be illustrated by  
20 concentration responses to  $\alpha$ 4 $\beta$ 2 agonists, for example 5-[(2R)-azetidin-2-ylmethoxy]-2-chloropyridine (Compound A) and (3R)-1-pyridin-3-ylpyrrolidin-3-amine (Compound B), in presence of a fixed concentration of PAM. As shown in Figures 1A and 2A, in the presence of an  $\alpha$ 4 $\beta$ 2PAM (for example, 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile (Compound 1) at 10  $\mu$ M), the concentration-responses to  $\alpha$ 4 $\beta$ 2agonists, for example 5-[(2R)-  
25 azetidin-2-ylmethoxy]-2-chloropyridine (Compound A) and (3R)-1-pyridin-3-ylpyrrolidin-3-amine (Compound B), are shifted typically by 1 - 2 log units (10-100-fold) to the left resulting in more potent EC<sub>50</sub> values to agonists. In addition to compound A and B, other known nicotinic agonists can be left-shifted in presence of  $\alpha$ 4 $\beta$ 2 PAM such as 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile (Compound 1, Figure 2C). When these experiments  
30 are done with cells expressing other nAChR subunits such as  $\alpha$ 3 $\beta$ 4 (see Figures 1B and 2B), the PAM is unable to affect the concentration responses to the agonists. This shows that PAMs can selective enhance potency of the compound selectively at  $\alpha$ 4 $\beta$ 2, but not other (e.g.  $\alpha$ 3 $\beta$ 4) subtypes. This could lead to preferential effects of the agonist at the desired subtype,

viz.,  $\alpha 4\beta 2$ , without effects at other nicotinic receptor subtypes and thus enhancing in vivo selectivity of the agonist.

Table 1 lists the results for the compounds of the present invention. The activity (allosteric effects – potentiation of fluorescence responses) ranges are defined as follows; “a” denotes as activity range from 200 – 400%, “b” denotes an activity range from 150-200%, “c” denotes an activity range from 120-150% and “d” denotes an activity range 90-120%.

Table 1. Examples of Selected  $\alpha 4\beta 2$  positive allosteric modulators

Example No.	Structure	Activity	Example No.	Structure	Activity
1		a	19		b
2		a	35		a
3		a	40		a
4		b	41		c
5		c	42		c
7		b	52		d
9		d	55		c
10		a	68		b
11		a	76		b

125		a	83		a
101		a	132		a

Example B:  $\alpha 4\beta 2$  Positive allosteric modulator enhances the effects of nicotinic ligands with very low intrinsic agonist efficacy.

*Calcium Flux Assays*: HEK-293 cells stably expressing human  $\alpha 4\beta 2$  or  $\alpha 3\beta 4$  are to confluency in 162 cm<sup>2</sup> tissue culture flasks in DMEM media supplemented with 10% FBS and 25  $\mu$ g/ml zeocin and 200  $\mu$ g/ml hygromycin B. IMR-32 neuroblastoma cells (ATCC) are grown to confluency in 162 cm<sup>2</sup> tissue culture flasks in minimum essential media supplemented with 10% FBS and 1 mM sodium pyruvate, 1 % non-essential amino acids and 1% antibiotic-antimycotic. The cells are then dissociated using cell dissociation buffer and 100-150  $\mu$ l per well of  $3.5 \times 10^5$  cells/ml cell suspension (~50,000 –100,000 cells/well) was plated into 96-well black plates (poly-D-lysine precoated) with clear bottom and maintained for 24-48 hours in a tissue culture incubator at 37°C under an atmosphere of 5% CO<sub>2</sub>: 95% air. Other clonal cell lines or dissociated primary cortical neurons that express endogenous  $\alpha 4^*$  nicotinic receptors may also be used in this assay. Calcium flux was measured using calcium-3 assay kit (Molecular Devices, Sunnyvale, CA) or fluo-4 (Invitrogen). A stock solution of the dye was prepared by dissolving each vial supplied by the vendor in Hank's balanced salt solution buffer (HBSS) or 150 mM NMDG, 20 mM CaCl<sub>2</sub> containing 10 mM HEPES. The stock solution was diluted 1:20 using the same buffer before use. The growth media was removed from the cells. The cells were loaded with 100  $\mu$ l of the dye per well and incubated at room temperature for up to one hour for HEK 293 clonal stable cell lines or 30 minutes – 45 minutes at 37 °C for IMR-32 cells. Fluorescence measurements were read simultaneously from all the wells by a Fluorometric Imaging Plate Reader (FLIPR) at an excitation wavelength of 480 nm and an emission wavelength of 520 nm. Baseline fluorescence was measured for the first 6 seconds at which 3X concentrations of modulator/test compounds were added to the cell plate at 50  $\mu$ l and incubated for five minutes. The fluorescence intensity was captured every second for the first 1 minute followed by every 5 seconds for an additional 4 minutes. This procedure was followed by 50

μl of 4X concentration of agonist and readings were taken for a period of 3-5 minutes as described above. Data was normalized to maximal responses and plotted as a function of concentration. The concentration dependence of changes fluorescence responses was fitted by nonlinear regression analysis (GraphPad Prism, San Diego, CA) to obtain EC<sub>50</sub> values.

5           α4β2 PAMs can also enhance the efficacy of partial agonists (compounds that bind, but activate α4β2 nAChRs with low intrinsic efficacy leading to otherwise barely detectable effects on calcium responses). For example, responses to 2-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine (Compound C) in the presence and absence of PAM is shown in Figure 3. The results show in the presence of an α4β2 PAM (for example, 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile (Compound 1)), the maximum fluorescence calcium  
10           signal was substantially enhanced to application of 2-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine at the α4β2 receptor (Figure 3A), but again, not at the α3β4 receptor (Figure 3B). Another example is provided by Compound D, (1S,5S)-3-(3,6-diaza-bicyclo[3.2.0]hept-3-yl)-quinoline; compound with toluene-4-sulfonic acid which also binds  
15           to α4β2 nAChR ([<sup>3</sup>H]cyt Ki = 6 nM), but does not show substantial calcium responses alone; however, when co-incubated with α4β2 PAM, responses are substantially enhanced at α4β2 nAChR (Figure 4A), but not at α3β4 nAChRs (Figure 4B). These observations provides mechanistic support for compounds like 2-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine and (1S,5S)-3-(3,6-Diaza-bicyclo[3.2.0]hept-3-yl)-quinoline being more effective when co-  
20           applied with the PAM. The potentiation of α4β2 effects by PAM may potential for optimizing and enhancing efficacy in indications such as ADHD, cognitive deficits, Alzheimer's disease, and pain.

Figure 5 shows a comparison of EC<sub>50</sub> values from calcium fluorescence (FLIPR) assays using α4β2 nAChRs of several nicotinic agonists including varenicline and  
25           ispronicline in the presence and absence of positive allosteric modulator. The potency (EC<sub>50</sub> values) of the nicotinic agonists increase in the presence of the positive allosteric modulator.

Example C: α4β2 PAM enhances the efficacy of Compound A in an *in vivo* model of neuropathic pain.

30           To assess whether α4β2 PAM can increase antinociceptive responses of agonists *in vivo*, the following study was conducted. The materials and methods used to accomplish the study follow.

*Animals:* Male Sprague-Dawley rats (Charles River, Wilmington, MA) weighing 120-150 grams at time of surgery were utilized. These animals were group housed in AAALAC approved facilities at Abbott Laboratories in a temperature-regulated environment with lights on between 0700 and 2000 hours. Food and water was available *ad libitum* except during testing. All animal handling and experimental protocols were approved by an institutional animal care and use committee (IACUC). All experiments were performed during the light cycle.

*Chemicals:* 5-[(2R)-Azetidin-2-ylmethoxy]-2-chloropyridine (Compound A, 1-100 nmol/kg) and 3-(3-pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile ( $\alpha 4\beta 2$  PAM Compound 1, 1-35  $\mu\text{mol/kg}$ , i.p.) was used. Compound A and D was prepared in saline and injected in solution in a volume of 2 ml/kg body weight 30 minutes before behavioral evaluation. Compound 1, 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile, was prepared in 30% hydroxybetacyclodextrin and injected in solution in a volume of 4 ml/kg body weight immediately before Compound A. For studies with Compound D, the doses tested ranged from 0.3 - 30  $\mu\text{mol/kg}$  i.p.

*Experimental Procedure:* To produce neuropathic pain, tight ligation of the L5-L6 spinal nerves was performed. As previously described in detail by Kim and Chung (Kim SH and Chung JM (1992), Pain 50: 355), following sterilization procedures, a 1.5 cm incision was made dorsal to the lumbosacral plexus. The paraspinal muscles (left side) were separated from the spinous processes, the L5 and L6 spinal nerves isolated, and tightly ligated with 3-0 silk thread. Following hemostasis, the wound was sutured and coated with antibiotic ointment. The rats were allowed to recover and then placed in a cage with soft bedding for 7-14 days before behavioral testing for mechanical allodynia.

Tactile allodynia was measured using calibrated (force; g) von Frey filaments (Stoelting, Wood Dale, IL). Briefly, rats were placed into individual plexiglass containers and allowed to acclimate for 15-20 minutes before testing. Withdrawal threshold was determined by increasing and decreasing stimulus intensity and estimated using a Dixon non-parametric test (Chaplan et al., 1994; Chaplan SR, Bach FW, Pogrel JW, Chung JM and Yaksh TL (1994) J Neurosci Methods 53:55-63). Only rats with threshold scores  $\leq 4.5$  g were considered allodynic and utilized in further testing. A percent of maximal possible effect (% M.P.E.) of the tested compounds was calculated according to the formula:  $([\text{post-drug threshold}] - [\text{baseline threshold}] / ([\text{maximum threshold}] - [\text{baseline threshold}]) \times 100\%$ , where maximum threshold was equal to 15 g.

*Statistical analysis:* Analysis of the *in vivo* data was carried out using analysis of variance. Where appropriate, Bonferroni's Multiple Comparison Test was used for post-hoc analysis. The level of significance was set at  $p$  less than 0.05. Data are presented as mean  $\pm$  S.E.M.

5           *Results:* As shown in Figure 6A, tight ligation of L5-L6 spinal nerves induced pronounced mechanical allodynia with a decrease in mechanical paw withdrawal threshold (PWT) in the vehicle group to  $2.6 \pm 0.4$ g. Compound 1, 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile (PAM, 10 mg/kg, i. p.) did not produce significant reversal of nerve injury induced mechanical allodynia (PWT:  $3.3 \pm 0.4$ g,  $P$  greater than 0.05 vs. vehicle group).  
10           Compound A ( $0.03 \mu\text{mol/kg}$ , i.p.) produced weak but significant reversal of mechanical allodynia (PWT:  $5.6 \pm 0.3$ g,  $P$  less than 0.001 vs. vehicle group). When co-administered, Compound A + 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile (Compound 1, PAM) produced a pronounced reversal of nerve injury-induced mechanical allodynia (PWT:  $12.1 \pm 0.5$ g) that was significantly different from vehicle ( $P$  less than 0.001), but also from  
15           Compound A alone ( $P$  less than 0.001) and 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile, Compound 1, alone ( $P$  less than 0.001). This study demonstrates that the co-administration of a  $\alpha 4\beta 2$  positive allosteric modulator to a  $\alpha 4\beta 2$  agonist potentiate the antiallodynic effects of the agonist. Since the efficacy of the  $\alpha 4\beta 2$  ligand in neuropathic pain is robustly improved in presence of a PAM, an overall improvement in therapeutic window  
20           for the treatment of pain may be envisaged utilizing a combination approach (agonist in combination with the  $\alpha 4\beta 2$  PAM).

            Figure 6B shows that the effects of PAM (3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile, Compound 1) are dose-dependent. An ineffective dose of Compound A ( $1 \text{ nmol/kg}$ ), when combined with varying doses of PAM (3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile, Compound 1) results in dose-dependent increase in efficacy, approaching at  
25           least that of gabapentin, a drug clinically used for the treatment of neuropathic pain.

            Figure 7A shows dose dependent effects in neuropathic pain of 5-[(2R)-azetidin-2-ylmethoxy]-2-chloropyridine (Compound A) alone,  $\alpha 4\beta 2$  PAM (3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile, Compound 1) alone and a combination of Compound 1 ( $3.5 \mu\text{mol/kg}$ ) with various doses of Compound A.  $\alpha 4\beta 2$  PAM (Compound 1) alone is  
30           ineffective, but is capable of left-shifting the dose response curve of Compound A in the Chung model of neuropathic pain.

Example D: Analysis of compound effects on emesis in ferrets.

Fasted male ferrets (Marshall BioResources, North Rose, NY) weighing between 1.0 and 1.7 kg are used to determine the emetic effects.  $\alpha 4\beta 2$  PAM (Compound 1) was administered first and thirty minutes later, Compound A was administered at various doses. After dosing, the animals were observed for emesis and behaviors characteristic of nausea for a period of 90 minutes. The percentage of animals that experienced emesis at a given dose was recorded.

Figure 7B shows effects on emesis. Shown are effects of 5-[(2R)-azetidin-2-ylmethoxy]-2-chloropyridine (Compound A) alone,  $\alpha 4\beta 2$  PAM (Compound 1) alone and a combination of Compound 1 (3.5  $\mu\text{mol/kg}$ ) with various doses of compound A.  $\alpha 4\beta 2$  PAM (Compound 1) alone does not cause emesis, and does not shift the dose response curve of Compound A in the ferret model of emesis.

Figures 8A and 8B show plasma level analysis in models of neuropathic pain and emesis. Note the left ward shift in efficacy of Compound A in Figure 8A, but no shift in effects on emesis in Figure 8B. In other words, maximal efficacy of Compound A can be realized in neuropathic pain without incidence of emesis, in presence of  $\alpha 4\beta 2$  PAM (Compound 1), thus widening the therapeutic window of  $\alpha 4\beta 2$  nAChR agonists

Example E:  $\alpha 4\beta 2$  Partial agonists can be effective in reversing neuropathic pain in the presence of  $\alpha 4\beta 2$  positive allosteric modulators

To further examine effects in neuropathic pain, the effects of Compound D, another  $\alpha 4\beta 2$  ligand with low intrinsic efficacy (partial agonist) was examined in the Chung model. Alone, Compound D is ineffective in reversing neuropathic pain, but when combined with the PAM (Compound 1), significant efficacy can be realized. Figure 9 shows the efficacy of partial agonist, Compound D in the presence and absence of  $\alpha 4\beta 2$  PAM (Compound 1). Compound D when administered alone is ineffective in relieving pain. When co-dosed with  $\alpha 4\beta 2$  PAM (Compound 1), Compound D is now effective, and shows significant relief of neuropathic pain in rats. As shown previously, PAM (Compound 1) alone is ineffective (P+V).

Example F:  $\alpha 4\beta 2$  PAM enhances the efficacy of Compound A in an *in vivo* model of monoiodoacetate-induced osteoarthritis pain.

Monoiodoacetate-induced osteoarthritis (MIA-OA) Model.

Under light isoflurane (2-3%) anesthesia, MIA (3 mg) was unilateral intra-articularly injected into right hind knee joint in a volume of 50  $\mu$ l as previously described (Chandran *et al.*, 2009). Compressive grip force (CGF) was determined 20 days following MIA injection by recording the maximum compressive force exerted on the hind limb strain gauge setup, using a commercially available grip force measurement system (Columbus Instruments, Columbus, OH). In this assay, each rat was gently restrained and the hind paw was allowed to grasp the wire mesh frame (10 x 12 cm) attached to the strain gauge. The animal was then moved in a rostral-to-caudal direction until the grip was broken, and CGF reading expressed as g was recorded. Each rat was sequentially tested twice at approximately 2-3 min intervals to obtain an average raw CGF. To avoid confounding factor of body weight, CGF was converted into  $CGF_{body}$  following the formula:  $g (CGF) \div kg (body weight)$ . CGF was assessed 30 min following i.p. compound administration. The vehicle control group was taken as 0%, whereas the age-matched naïve group was described as 100% (normal), the analgesic efficacy was expressed as the percentage return of  $CGF_{body}$  to normalcy vs. the naïve group:  $[(treatment - vehicle) / (naïve - vehicle)] \times 100\%$ . Experiments were performed in animals 20 days following MIA knee joint injection, since this is the time point that maximal reduction of grip force observed in the time-course experiment (Chandran *et al.*, 2009).

*Results:* The effects of 5-[(2R)-azetidin-2-ylmethoxy]-2-chloropyridine (Compound A) or co-administration of Compound A with PAM 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile (Compound 1) on return of the grip force normalcy were investigated in rats underwent MIA injection of the right knee joint.  $CGF_{body}$  was reduced in animals assessed 20 days following MIA injection of the right hind knee joint. Compound 1 at 3.5  $\mu$ mol/kg i.p. alone produced no return of grip force normalcy in OA rats (data not shown). As illustrated in Figure 11, Compound A at 1, 3, 10 and 30 nmol/kg increased  $CGF_{body}$  by  $575 \pm 37$ ,  $717 \pm 64$ ,  $992 \pm 45$  and  $1234 \pm 37$  g, respectively; in the presence of Compound 1 (3.5  $\mu$ mol/kg), Compound A at 0.3, 1, 3, and 10 nmol/kg/kg increased  $CGF_{body}$  by  $657 \pm 21$ ,  $855 \pm 28$ ,  $971 \pm 35$  and  $1243 \pm 56$  g, respectively; compared to  $397 \pm 29$  g in vehicle treated animals (Fig. 11,  $P < 0.01$ ,  $n = 7$  per group). Representing the raw data as a percent return of grip force to normalcy, Compound A at 1, 3, 10 and 30 nmol/kg demonstrated percent return of grip force to normalcy of  $20 \pm 4$ , and  $35 \pm 6$ ,  $65 \pm 5$ , and  $90 \pm 4\%$ , respectively (Fig. 3B,  $ED_{50} = 4.6$  nmol/kg); Compound A at 0.3, 1, 3, and 10, nmol/kg, combined with Compound 1 (3.5  $\mu$ mol/kg), produced percent return of grip force to normalcy of  $29 \pm 2$ ,  $50 \pm 3\%$ ,  $66 \pm 5\%$

and  $92 \pm 6\%$ , respectively (Fig. 3B,  $ED_{50} = 1 \text{ nmol/kg}$ ). Therefore, co-administration of Compound 1 revealed a leftward shift in the DRC of Compound A by 5-fold.

Example G: Carrageenan model of Acute inflammatory thermal hyperalgesia.

5 Acute inflammatory thermal hyperalgesia were induced by injecting 100  $\mu\text{l}$  of a 1% solution of  $\lambda$ -carrageenan (Sigma Chemical Co., St. Louis, MO) in physiological saline into the plantar surface of the right hind paw. Thermal hyperalgesia measured as paw withdrawal latency (PWL) was determined, using a commercially available thermal paw stimulator (UARDG, University of California, San Diego, CA) as described by Hargreaves et al.  
10 (Hargreaves *et al.*, 1988). Rats were placed into individual plastic cubicles mounted on a glass surface maintained at  $30^{\circ}\text{C}$ , where a thermal stimulus, in the form of radiant heat emitted from a focused projection bulb, was then applied to the plantar surface of each hind paw. The stimulus current was maintained at  $4.50 \pm 0.05 \text{ amp}$ , and the maximum time of exposure was set at 20.48 s to limit possible tissue damage. The elapsed time until a brisk  
15 withdrawal of the hind paw from the thermal stimulus was recorded automatically using photodiode motion sensors. The right (carrageenan injected paw) and left hind paw of each rat was tested in 3 sequential trials at approximately 5 min intervals. Carrageenan-induced thermal hyperalgesia of paw withdrawal latency ( $\text{PWL}_{\text{carra}}$ ) was calculated as the mean of the two shortest latencies. PWL was assessed 30 min (2 h after carrageenan injection) following  
20 i.p. compound administration.  $\text{PWL}_{\text{carra}}$  of the vehicle control group was taken as 0%, whereas the PWL of the contralateral side ( $\text{PWL}_{\text{contra}}$ ) of the vehicle control group was taken as 100%, the analgesic efficacy was expressed as the percentage return of  $\text{PWL}_{\text{carra}}$  to  $\text{PWL}_{\text{contra}}$ .

*Results:* The effects of 5-[(2R)-azetidin-2-ylmethoxy]-2-chloropyridine (Compound  
25 A) or co-administration of Compound A with PAM 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile (Compound 1) on carrageenan-induced acute inflammatory thermal hyperalgesia were examined behaviors were examined in rats underwent carrageenan injection into the hind paw. Hind paw injury resulted in the development of thermal hyperalgesia as indicated by a decreased  $\text{PWL}_{\text{carra}}$  to heat stimulus. Compound 1 (up to 35  
30  $\mu\text{mol/kg}$ , i.p.,  $P > 0.05$ ) alone produced no alteration of  $\text{PWL}_{\text{carra}}$ , compared to vehicle treated animals (data not shown). Compound A at 100 and 300  $\text{nmol/kg}$  i.p. increased  $\text{PWL}_{\text{carra}}$  to  $5.46 \pm 0.36$  and  $8.80 \pm 0.65 \text{ s}$ , compared to  $3.46 \pm 0.29 \text{ s}$  in vehicle treated animals ( $P < 0.01$ ,  $n = 18$  per group). The slight increase of the  $\text{PWL}_{\text{contra}}$  in Compound A treated animals was

not statistically significant, compared to that of vehicle treated animals. As illustrated in Figure 12, in the presence of Compound 1 (3.5  $\mu\text{mol/kg}$ ), Compound A at 10, 30 and 100 nmol/kg i.p. increased the  $\text{PWL}_{\text{contra}}$  to  $5.29 \pm 0.91$ ,  $6.35 \pm 0.71$  and  $8.94 \pm 0.79$  s, respectively, compared to  $3.17 \pm 0.25$  s in vehicle treated animals ( $P < 0.01$ ,  $n = 12$  per group). The slight increase of the  $\text{PWL}_{\text{contra}}$  in Compound A and co-administered animals was not statistically significant, compared to that of vehicle treated animals. Representing the raw data as a percent reversal of thermal hyperalgesia, Compound A at 100 and 300 nmol/kg demonstrated percent reversals of  $28 \pm 5$ , and  $74 \pm 9\%$ , respectively ( $\text{ED}_{50} = 160$  nmol/kg); Compound A at 10, 30 and 100 nmol/kg, combined with Compound 1 (3.5  $\mu\text{mol/kg}$ ), produced percent reversals of  $31 \pm 13$ ,  $46 \pm 10\%$  and  $84 \pm 12\%$ , respectively (Fig. 12,  $\text{ED}_{50} = 30$  nmol/kg). Therefore, co-administration of Compound 1 revealed a leftward shift in the DRC of Compound A by 5-fold.

#### Example H: Incision Model of Postoperative Pain.

Paw incision was performed under isoflurane (2-3%) anesthesia and followed procedures previously described (Brennan *et al.*, 1996). Briefly, the plantar aspect of the left hindpaw was placed through a hole in a sterile plastic drape. A 1-cm longitudinal incision was made through the skin and fascia, starting 0.5 cm from the proximal edge of the heel and extending towards the toes, the plantar muscle was elevated and injured longitudinally leaving the muscle origin and insertion points intact. After hemostasis with gentle pressure, the skin was apposed with 2 mattress sutures of 5-0 nylon. Mechanical allodynia was measured using calibrated von Frey filaments (Stoelting, Wood Dale, IL) as previously described (Chaplan *et al.*, 1994) in all animals 2 h following surgery. Rats were placed into inverted individual plastic containers (20 x 12.5 x 20 cm) on top of a suspended wire mesh grid, and acclimated to the test chambers for 20 min. The von Frey filaments were presented perpendicularly to the plantar surface pointing towards the medial side of the incision (Brennan *et al.*, 1996), and then held in this position for approximately 8 s with enough force to cause a slight bend in the filament. Positive responses included an abrupt withdrawal of the hind paw from the stimulus, or flinching behavior immediately following removal of the stimulus. A 50% paw withdrawal threshold (PWT) was determined using an up-down procedure (Dixon, 1980). Mechanical allodynia was assessed 30 min following i.p. compound administration.

*Results:* The effects of 5-[(2R)-azetidin-2-ylmethoxy]-2-chloropyridine (Compound A) or co-administration of Compound A with PAM 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile (Compound 1) on post-operative pain behaviors were examined in rats underwent skin incision of the hind paw. Hind paw injury resulted in the development of mechanical allodynia as indicated by a decreased PWT to a series of mechanical stimuli of calibrated von Frey filament 2 hr post-incision. (Compound 1 (up to 35  $\mu\text{mol/kg}$ , i.p.) alone produced no alteration of PWT of the injured paw, compared to vehicle treated animals (data not shown). Compound A at 100 and 300  $\text{nmol/kg}$  increased PWT to  $6.0 \pm 1.0$  and  $12.0 \pm 1.6$  g, compared to vehicle-treated group of  $3.0 \pm 0.3$  (Fig 2A,  $P < 0.01$ ,  $n = 6$  per group); in the presence of Compound 1 (3.5  $\mu\text{mol/kg}$ ), Compound A at 10, 30 and 100  $\text{nmol/kg}$  increased PWT to  $5.0 \pm 1.9$ ,  $9.2 \pm 2.1$  and  $13.1 \pm 1.2$  g, compared to vehicle-treated group of  $2.3 \pm 0.2$  g (Fig 2B,  $P < 0.01$ ,  $n = 6$  per group). Representing the raw data as a percent reversal of mechanical allodynia, Compound A at 100 and 300  $\text{nmol/kg}$  demonstrated percent reversals of  $25 \pm 8$ , and  $75 \pm 12\%$ , respectively (Fig. 13,  $\text{ED}_{50} = 165$   $\text{nmol/kg}$ ); Compound A at 10, 30 and 100  $\text{nmol/kg}$ , combined with Compound 1 (3.5  $\mu\text{mol/kg}$ ), produced percent reversals of  $22 \pm 14$ ,  $54 \pm 16\%$  and  $85 \pm 10\%$ , respectively (Fig. 13,  $\text{ED}_{50} = 26$   $\text{nmol/kg}$ ). Therefore, as illustrated in Figure 13, co-administration of Compound 1 revealed a leftward shift in the DRC of Compound A by 6-fold.

#### Characterization of Nicotinic Acetylcholine Receptor Ligands

In addition to the assays previously described for assessing nicotinic acetylcholine receptor positive allosteric modulators (fluorescence-based measurements, electrophysiology measurements using *Xenopus* oocytes or cell lines), the receptor interactions of positive allosteric modulators at  $\alpha 4\beta 2$  nAChRs also can be evaluated according to the [ $^3\text{H}$ ]-POB binding assay, which was performed as described below.

#### [ $^3\text{H}$ ]-3-(5-(Pyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzotrile ([ $^3\text{H}$ ]-POB) Binding

[ $^3\text{H}$ ]-POB ([ $^3\text{H}$ ]-3-(5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzotrile) binding to a  $\alpha 4\beta 2$ nAChR modulator site was determined using membrane enriched fractions from human cortex (ABS Inc., Wilmington, DE). Pellets were thawed at 4  $^{\circ}\text{C}$ , washed and resuspended with a Polytron at a setting of 7 in 30 volumes of BSS-Tris buffer (120 mM NaCl, 5 mM

KCl, 2 mM CaCl<sub>2</sub>, 2 mM MgCl<sub>2</sub>, and 50 mM Tris-Cl, pH 7.4, 4 °C). For saturation binding isotherms, eight concentrations of [<sup>3</sup>H]-POB (10-250 nM) in quadruplicate and homogenate containing 100-200 µg of protein were incubated in a final volume of 500 µL for 75 minutes at 4 °C. Non-specific binding was determined in the presence of 30 µM unlabeled 3-(5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzotrile. Under these conditions, saturable binding of [<sup>3</sup>H]-POB binding was measured in membrane enriched fractions from human frontal cortex (Figure 10). The K<sub>d</sub> and B<sub>max</sub> values were 60 ± 16 nM and 2900 ± 500 fmol/mg protein, respectively. Membrane preparations from other species (rat, mouse, ferret) and from clonal or transfected cell lines that express α4β2 nAChRs cloned from various species may also be used in this binding assay.

For use in concentration-inhibition assays, seven log-dilution concentrations of test compounds containing 100-200 µg of protein, and 50 nM [<sup>3</sup>H]-POB (16.4 Ci/mmol) were incubated in a final volume of 500 µL for 75 minutes at 4 °C in duplicate. Non-specific binding was determined in the presence of 30 µM 3-(5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzotrile. Bound radioactivity was collected on Millipore MultiScreen® harvest plates FB presoaked with 0.3% polyethyleneimine using a PerkinElmer cell harvester, washed with 2.5 mL of ice-cold buffer, and radioactivity was determined using a PerkinElmer TopCount Microplate beta counter. Dissociation constant (K<sub>d</sub>) and maximum binding (B<sub>max</sub>) values from saturation binding experiments were determined using GraphPad Prism (Graphpad Software, San Diego, CA). IC<sub>50</sub> values were determined by nonlinear regression in Microsoft® Excel or Assay Explorer. K<sub>i</sub> values were calculated from the IC<sub>50</sub>s using the Cheng-Prusoff equation, where  $K_i = IC_{50}/(1+[Ligand]/K_D)$ .

[<sup>3</sup>H]-POB was obtained according to the preparation procedures generally described in Example 135 shown below.

#### Example 135

[<sup>3</sup>H]-3-(5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzotrile

#### Example 135A

3-(5-(5-bromopyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzotrile

The title compound was prepared according to the procedure of Example 4B using 3-cyano-N'-hydroxybenzimidamide and 5-bromonicotinoyl chloride (Alfa). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.67 (m, 1 H), 7.74 (m, 1 H), 8.41 (m, 1 H), 8.49 (m, 1 H), 8.64 (s, 1 H), 8.93 (s, 1 H), 9.4 (s, 1 H) ppm; MS (DCI/NH<sub>3</sub>) m/z 327 (M+H)<sup>+</sup>.

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#### Example 135B

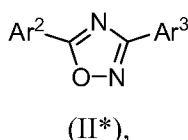
##### [<sup>3</sup>H]-3-(5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzotrile ([<sup>3</sup>H]-POB)

The compound of Example 135A was dissolved in a mixture of dichloromethane, triethylamine, and 5% palladium on carbon. The reaction solution was then saturated with tritium gas (1.2 Ci). The reaction mixture was stirred at room temperature for 3.5 hours, the catalyst was removed by filtration, and the filtrate was concentrated to yield crude tritiated product. Further purification of the crude material by reverse-phase HPLC using a 30 minute 40% isocratic acetonitrile run (column LunaC18, 254 nm) to provide a total of 200 mCi (1 mL, methanol).

The radiochemical purity of [<sup>3</sup>H]-POB was found to be 99% and the specific activity was determined to be 16.4 Ci/mmol.

Nicotinic acetylcholine receptor ligands suitable for the invention exhibit K<sub>i</sub> values ranging about 1 nanomolar to about 10 micromolar when tested by the [<sup>3</sup>H]-POB assay, many having a K<sub>i</sub> of less than 5 micromolar. Compounds that modulate the function of α4β2nAChRs by altering the activity of the receptor or signaling are suitable for the composition. More specifically, the compounds that function as allosteric modulators enhancing the efficacy and/or potency of acetylcholine or a nicotinic agonist are desired. Multiple binding sites at α4β2 nAChRs may exist for such compounds, of which only one site may be defined by [<sup>3</sup>H]POB binding.

Also contemplated is compound of formula(II\*):



wherein Ar<sup>2</sup> is aryl or heteroaryl, wherein the aryl or heteroaryl is substituted or unsubstituted, and, when substituted, the aryl or heteroaryl is substituted with 1, 2, 3, or 4 substituents selected from halo, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>6</sub>-C<sub>10</sub> aryl, C<sub>4</sub>-C<sub>7</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>5</sub>-C<sub>10</sub> heteroaryl, C<sub>4</sub>-C<sub>10</sub> heterocycle, C<sub>1</sub>-C<sub>6</sub> alkyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl)NHC(O)O-(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl, amino, hydroxyl,

haloalkyl-C(O)-, haloalkyl-SO<sub>2</sub>-, alkyl-SO<sub>2</sub>-, -SO<sub>2</sub>NH<sub>2</sub>, -SO<sub>2</sub>NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -SO<sub>2</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, cyano, nitro, C<sub>1</sub>-C<sub>6</sub> acylamino, C<sub>1</sub>-C<sub>6</sub> alkoxy, -C(O)NH<sub>2</sub>, -C(O)O-(C<sub>1</sub>-C<sub>6</sub> alkyl), and carboxy; and

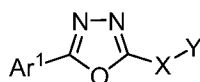
Ar<sup>3</sup> is aryl or heteroaryl, wherein the aryl or heteroaryl is substituted or unsubstituted, and, when substituted, the aryl or heteroaryl is substituted with a substituent selected from halo, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>6</sub>-C<sub>10</sub> aryl, C<sub>4</sub>-C<sub>7</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>5</sub>-C<sub>10</sub> heteroaryl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, amino, hydroxyl, haloalkyl-SO<sub>2</sub>-, cyano, nitro, C<sub>1</sub>-C<sub>6</sub> acylamino, C<sub>1</sub>-C<sub>6</sub> alkoxy, -N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, and carboxy; wherein at least one of the available atoms within a compound of formula (II\*) is replaced with a radioisotope. A particular radiolabelled compound of formula (II\*) is [<sup>3</sup>H]-3-(5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzotrile. Such compounds are suitable for use in determining the binding affinity of nicotinic acetylcholine receptor subtype α4β2 positive allosteric modulators.

Another embodiment of the invention is a radiolabeled compound of formula (II\*), wherein Ar<sup>2</sup> and Ar<sup>3</sup> are independently phenyl, pyrazinyl, pyridinyl, pyrimidinyl, pyridazine, triazinyl, or a bicyclic heteroaryl, substituted independently with 0, 1, 2, 3, or 4 substituents selected from the group consisting of alkoxy, alkoxy carbonyl, alkoxy carbonylamino, alkoxy carbonylaminoalkyl, alkyl, alkylamino, alkyl carbonyl, alkylsulfonyl, amido, amino, aminoalkyl, carboxy, dialkylamino, dialkylaminoalkyl, halo, haloalkyl, haloalkyl carbonyl, heteroaryl, heterocycle, hydroxy, hydroxyalkyl, cyano, nitro, sulfonamide and dialkylsulfonylformimidamide; provided that when one of Ar<sup>2</sup> and Ar<sup>3</sup> is pyridinyl or aryl, the other is not pyridinyl; when Ar<sup>3</sup> is pyridinyl, Ar<sup>2</sup> is not pyrazinyl.

It is understood that the foregoing detailed description and accompanying examples are merely illustrative and are not to be taken as limitations upon the scope of the invention, which is defined solely by the appended claims and their equivalents. The compositions, methods, and articles of manufacture have been described with reference to various specific embodiments and techniques. However, various changes and modifications, including without limitation those relating to the compounds, substituents, syntheses, and/or methods of use of the invention, may be made without departing from the spirit and scope thereof. The examples described herein are intended only to illustrate and do not limit the scope of the invention as defined in the appended claims and equivalents thereof.

## WHAT IS CLAIMED IS:

1. A composition for treating or preventing pain in a patient, the composition  
 5 comprising:
- (i) a nicotinic acetylcholine receptor ligand and
  - (ii) a nicotinic acetylcholine receptor subtype  $\alpha 4\beta 2$  positive allosteric modulator in admixture with at least one pharmaceutically acceptable excipient.
- 10 2. The composition of claim 1, wherein the nicotinic acetylcholine receptor ligand is a nicotinic acetylcholine receptor subtype  $\alpha 4\beta 2$  ligand demonstrating a  $K_i$  value that as measured by [ $^3\text{H}$ ]-cytisine binding assay ( $K_i$  Cyt) of about 0.001 nanomolar to about 100 micromolar.
- 15 3. The composition of claim 1, wherein the nicotinic acetylcholine receptor ligand is a nicotinic acetylcholine receptor subtype  $\alpha 4\beta 2$  agonist or partial agonist.
4. The composition of claim 1, wherein the nicotinic acetylcholine receptor ligand is a compound selected from:
- 20 5-[(2R)-azetidin-2-ylmethoxy]-2-chloropyridine,  
 (3R)-1-pyridin-3-ylpyrrolidin-3-amine, and  
 2-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine;  
 3-(5,6-dichloro-pyridin-3-yl)-1(S),5(S)-3,6-diazabicyclo[3.2.0]heptane; and  
 (R,R)-1-(pyridin-3-yl)octahydro-pyrrolo[3,4-b]pyrrole;
- 25 or is a pharmaceutically acceptable salt thereof.
5. The composition of claim 1, wherein the nicotinic acetylcholine receptor subtype  $\alpha 4\beta 2$  positive allosteric modulator has a formula:



30

or is a pharmaceutically acceptable salt or prodrug thereof, wherein

X is a bond, O, NR<sup>1</sup>, S, or C<sub>1</sub>-C<sub>3</sub> alkylene;

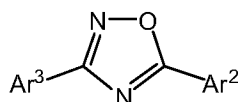
Y represents a monocyclic aryl, cycloalkyl, heterocycle, or heteroaryl group;

Ar<sup>1</sup> represents a monocyclic aryl or heteroaryl group; and

R<sup>1</sup> is hydrogen, alkyl, haloalkyl or arylalkyl.

5

6. The composition of claim 1, wherein the nicotinic acetylcholine receptor subtype  $\alpha 4\beta 2$  positive allosteric modulator is a compound of formula (II):



(II),

10

or a pharmaceutically acceptable salt thereof, wherein:

Ar<sup>2</sup> and Ar<sup>3</sup> are independently aryl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, triazinyl, or bicyclic heteroaryl, substituted independently with 0, 1, 2, 3, or 4 substituents selected from the group consisting of alkoxy, alkoxy carbonyl, alkoxy carbonylamino, alkoxy carbonylaminoalkyl, alkyl, alkylamino, alkyl carbonyl, alkylsulfonyl, amido, amino, aminoalkyl, carboxy, dialkylamino, dialkylaminoalkyl, halo, haloalkyl, haloalkyl carbonyl, heteroaryl, heterocycle, hydroxy, hydroxyalkyl, cyano, nitro, oxo, sulfonamide and dialkylsulfonylformimidamide; provided that when one of Ar<sup>2</sup> and Ar<sup>3</sup> is pyridinyl or aryl, the other is not pyridinyl; when Ar<sup>3</sup> is pyridinyl, Ar<sup>2</sup> is not pyrazinyl;

15

20

or a pharmaceutically acceptable salt thereof.

7. The composition of claim 5, wherein the nicotinic acetylcholine receptor subtype  $\alpha 4\beta 2$  positive allosteric modulator is selected from the group consisting of:

5-(2,3-difluorophenyl)-3-(pyrimidin-5-yl)-1,2,4-oxadiazole;

5-(pyridin-3-yl)-3-(pyrimidin-5-yl)-1,2,4-oxadiazole;

2-fluoro-*N,N*-dimethyl-4-(3-(pyrimidin-5-yl)-1,2,4-oxadiazol-5-yl)aniline;

3-(3-(pyrimidin-5-yl)-1,2,4-oxadiazol-5-yl)benzotrile;

5-(3,4-difluorophenyl)-3-(pyridazin-4-yl)-1,2,4-oxadiazole;

3-(pyridazin-4-yl)-5-(pyridin-3-yl)-1,2,4-oxadiazole;

*N,N*-dimethyl-*N'*-(4-(3-(pyrimidin-5-yl)-1,2,4-oxadiazol-5-yl)phenylsulfonyl)formimidamide;

5-(4-fluorophenyl)-3-(pyrimidin-5-yl)-1,2,4-oxadiazole;

30

- 5-(3-fluorophenyl)-3-(pyrimidin-5-yl)-1,2,4-oxadiazole;  
 3-(pyrimidin-5-yl)-5-(3,4,5-trifluorophenyl)-1,2,4-oxadiazole;  
 5-(2-chloropyridin-4-yl)-3-(pyrimidin-5-yl)-1,2,4-oxadiazole;  
 3-(Pyridin-3-yl)-5-(pyrimidin-5-yl)-1,2,4-oxadiazole;  
 5-(Pyridazin-4-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 3-(3-(pyridazin-4-yl)-1,2,4-oxadiazol-5-yl)benzotrile;  
 3-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzotrile;  
 5-(3-fluorophenyl)-3-(pyridazin-4-yl)-1,2,4-oxadiazole;  
 3-(pyridazin-4-yl)-5-(3,4,5-trifluorophenyl)-1,2,4-oxadiazole;  
 5-(3,5-difluorophenyl)-3-(pyridazin-4-yl)-1,2,4-oxadiazole;  
 5-(4-fluorophenyl)-3-(pyridazin-4-yl)-1,2,4-oxadiazole;  
 3-(pyridazin-4-yl)-5-(pyrimidin-5-yl)-1,2,4-oxadiazole;  
 3-(pyridazin-4-yl)-5-(2,3,6-trifluorophenyl)-1,2,4-oxadiazole;  
 3-(pyridazin-4-yl)-5-(2,3,4-trifluorophenyl)-1,2,4-oxadiazole;  
*N,N*-dimethyl-*N'*-(4-(3-(pyridazin-4-yl)-1,2,4-oxadiazol-5-yl) phenylsulfonyl) formimidamide;  
 5-(3,4-difluorophenyl)-3-(pyrimidin-5-yl)-1,2,4-oxadiazole;  
 3-(3,4-difluorophenyl)-5-(pyrimidin-5-yl)-1,2,4-oxadiazole;  
 3-(pyrimidin-5-yl)-5-(2,3,4-trifluorophenyl)-1,2,4-oxadiazole;  
 3-(pyrimidin-5-yl)-5-(2,3,6-trifluorophenyl)-1,2,4-oxadiazole;  
 3-(pyrimidin-5-yl)-5-(2,3,4,5-tetrafluorophenyl)-1,2,4-oxadiazole;  
 5-(imidazo[1,5-*a*]pyridin-6-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 5-(1*H*-indol-6-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 5-(2,7-dimethylpyrazolo[1,5-*a*]pyrimidin-6-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 5-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 5-(2-methylbenzofuran-5-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 5-(benzo[*d*][1,2,3]thiadiazol-5-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 5-(1*H*-benzo[*d*]imidazol-5-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 5-(1*H*-benzo[*d*][1,2,3]triazol-5-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 5-(benzo[*d*]thiazol-5-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 3-(pyridin-3-yl)-5-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1,2,4-oxadiazole;  
 5-(1*H*-indol-5-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 5-(benzofuran-5-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;

5-(1-methyl-1H-benzo[d]imidazol-5-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 3-(imidazo[1,2-a]pyridin-6-yl)-5-(pyridin-3-yl)-1,2,4-oxadiazole;  
 5-(6-chloropyridin-3-yl)-3-(imidazo[1,2-a]pyridin-6-yl)-1,2,4-oxadiazole;  
 5-(6-fluoropyridin-3-yl)-3-(imidazo[1,2-a]pyridin-6-yl)-1,2,4-oxadiazole;  
 5 5-(5-fluoropyridin-3-yl)-3-(imidazo[1,2-a]pyridin-6-yl)-1,2,4-oxadiazole;  
 5-(1*H*-indazol-5-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 5-([1,2,4]triazolo[4,3-*a*]pyridin-6-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 5-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzo[d]oxazol-2(3*H*)-one;  
 5-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)-1H-benzo[d]imidazole-2(3*H*)-thione;  
 10 1,3-dimethyl-5-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)-1H-benzo[d]imidazol-2(3*H*)-  
 one;  
 6-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzo[d]oxazol-2(3*H*)-one;  
 5-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)-1H-benzo[d]imidazol-2(3*H*)-one;  
 6-(3-(Pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzo[d]oxazol-2-amine;  
 15 6-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)benzo[d]oxazole;  
 5-(5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzo[d]oxazol-2(3*H*)-one;  
 5-(5-(6-chloropyridin-3-yl)-1,2,4-oxadiazol-3-yl)benzo[d]oxazol-2(3*H*)-one; and  
 5-(benzo[d][1,3]dioxol-5-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole;  
 or a pharmaceutically acceptable salt thereof.

8. A composition of claim 1, further comprising an effective amount of at least one of a non-steroid anti-inflammatory agent and an opioid.

9. A pharmaceutical composition comprising a therapeutically effective amount of a composition of claim 1 and a pharmaceutically acceptable carrier or excipient.

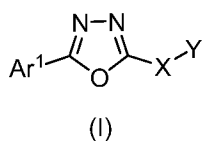
10. A method for treating a mammalian subject suffering from a pain condition, the method comprising administering a therapeutically effective amount of the composition of claim 1, wherein the pain condition is nociceptive pain, neuropathic pain or a combination thereof.

11. A method for treating a pain condition comprising administering a therapeutically effective amount of the composition of claim 10, wherein the nociceptive pain is selected

from post-operative pain, osteoarthritis pain, rheumatoid arthritis pain, musculoskeletal pain, burn pain, ocular pain, pain due to inflammation and bone fracture.

12. A method for treating or preventing a pain condition comprising administering (i) an amount of  $\alpha 4\beta 2$  nicotinic acetylcholine receptor ligand or a salt thereof; and (ii) an amount of a nicotinic acetylcholine receptor subtype  $\alpha 4\beta 2$  positive allosteric modulator, or a salt thereof, in admixture with at least one pharmaceutically acceptable excipient to a patient in need of treatment thereof.

13. The method of claim 12, wherein the nicotinic acetylcholine receptor subtype  $\alpha 4\beta 2$  positive allosteric modulator has a formula:



or is a pharmaceutically acceptable salt or prodrug thereof, wherein

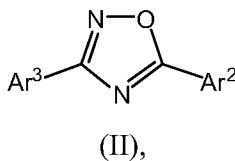
X is a bond, O, NR<sup>1</sup>, S, or C<sub>1</sub>-C<sub>3</sub> alkylene;

Y represents a monocyclic aryl, cycloalkyl, heterocycle, or heteroaryl group;

Ar<sup>1</sup> represents a monocyclic aryl or heteroaryl group; and

R<sup>1</sup> is hydrogen, alkyl, haloalkyl or arylalkyl.

14. The method of claim 12, wherein the nicotinic acetylcholine receptor subtype  $\alpha 4\beta 2$  positive allosteric modulator is a compound of formula (II):



or a pharmaceutically acceptable salt thereof, wherein:

Ar<sup>2</sup> and Ar<sup>3</sup> are independently aryl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, triazinyl, or bicyclic heteroaryl, substituted independently with 0, 1, 2, 3, or 4 substituents selected from the group consisting of alkoxy, alkoxy carbonyl, alkoxy carbonylamino, alkoxy carbonylaminoalkyl, alkyl, alkylamino, alkyl carbonyl, alkylsulfonyl, amido, amino,

aminoalkyl, carboxy, dialkylamino, dialkylaminoalkyl, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heterocycle, hydroxy, hydroxyalkyl, cyano, nitro, oxo, sulfonamide and dialkylsulfonylformimidamide; provided that when one of Ar<sup>2</sup> and Ar<sup>3</sup> is pyridinyl or aryl, the other is not pyridinyl; when Ar<sup>3</sup> is pyridinyl, Ar<sup>2</sup> is not pyrazinyl;  
or a pharmaceutically acceptable salt thereof.

15. The method of claim 14, wherein Ar<sup>2</sup> is cyanophenyl and Ar<sup>3</sup> is pyridin-3-yl.
16. The method of claim 12, wherein the nicotinic acetylcholine receptor ligand is 5-[(2R)-azetidin-2-ylmethoxy]-2-chloropyridine.
17. The method of claim 12, wherein the pain condition is nociceptive pain, neuropathic pain or a combination thereof.
18. The method of claim 17, wherein the nociceptive pain is osteoarthritis pain.
19. The method of claim 17, wherein the nociceptive pain is post-operative pain.
20. The method of claim 17, wherein the pain condition is hyperalgesia.
21. The method of claim 17, wherein the neuropathic pain is associated with a condition selected from herpes, HIV, traumatic nerve injury, stroke, post-ischemia, fibromyalgia, reflex sympathetic dystrophy, complex regional pain syndrome, spinal cord injury, sciatica, phantom limb pain, diabetic neuropathy, and cancer.
22. The method of claim 12, further comprising administering an effective amount of at least one of a non-steroid anti-inflammatory agent and an opioid.
23. A method for treating osteoarthritis pain, the method comprising administering a combination of a nicotinic acetylcholine receptor ligand and a nicotinic acetylcholine receptor subtype  $\alpha 4\beta 2$  positive allosteric modulator in a therapeutically effective amount to a patient in need thereof.

24. An article of manufacture for the treatment of pain, comprising:
- (i) a first pharmaceutical dosage form comprising at least one nicotinic acetylcholine receptor ligand; and
  - (ii) a second pharmaceutical dosage form comprising at least nicotinic acetylcholine receptor subtype  $\alpha 4\beta 2$  positive allosteric modulator; wherein the article contains first and second pharmaceutical dosage forms.

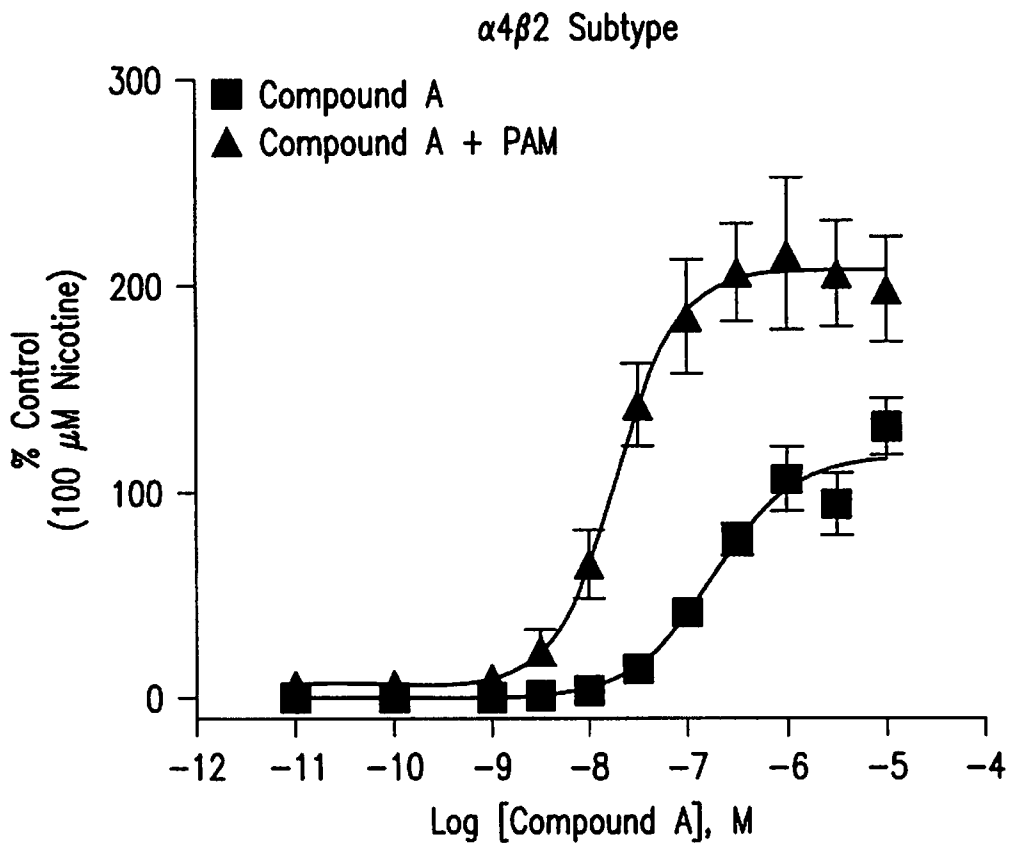


FIG.1A

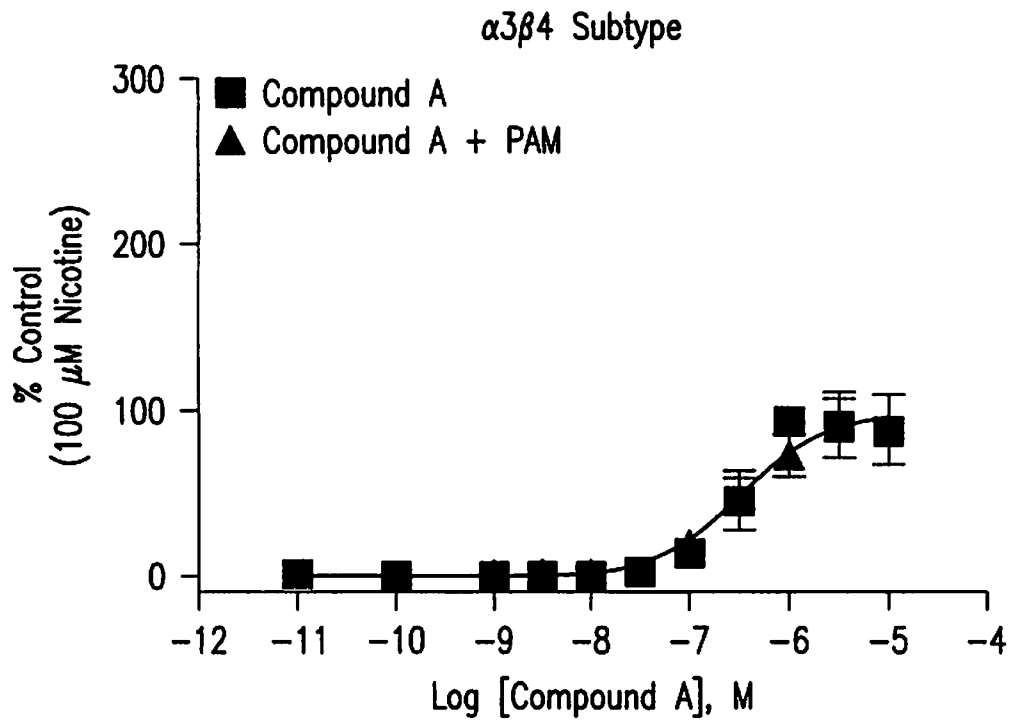


FIG.1B

3/20

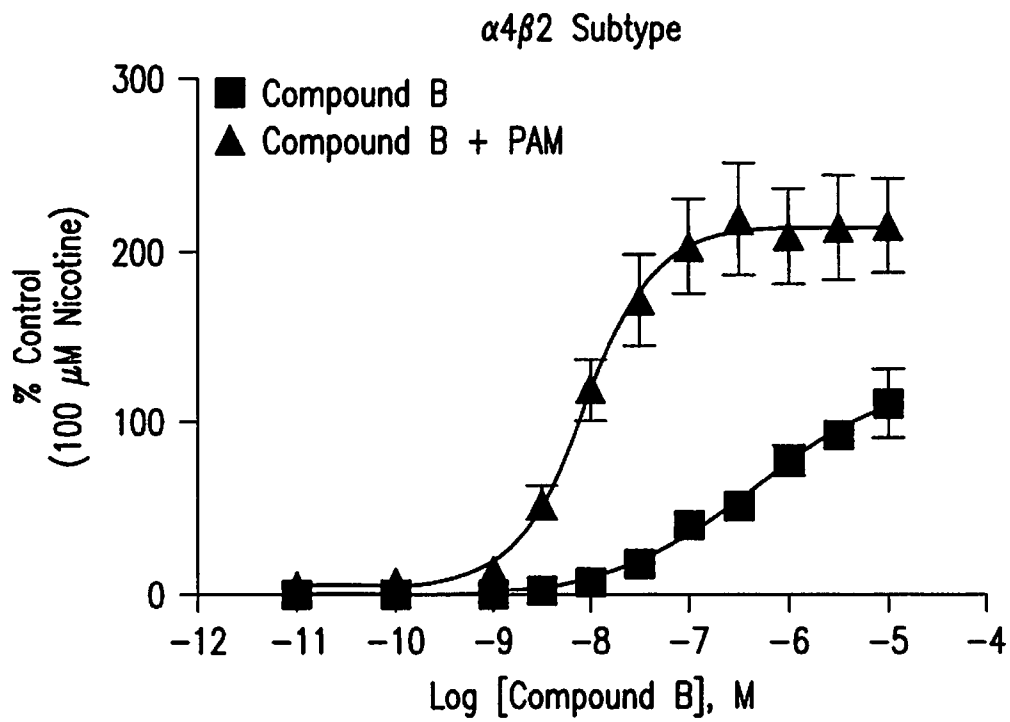


FIG.2A

4/20

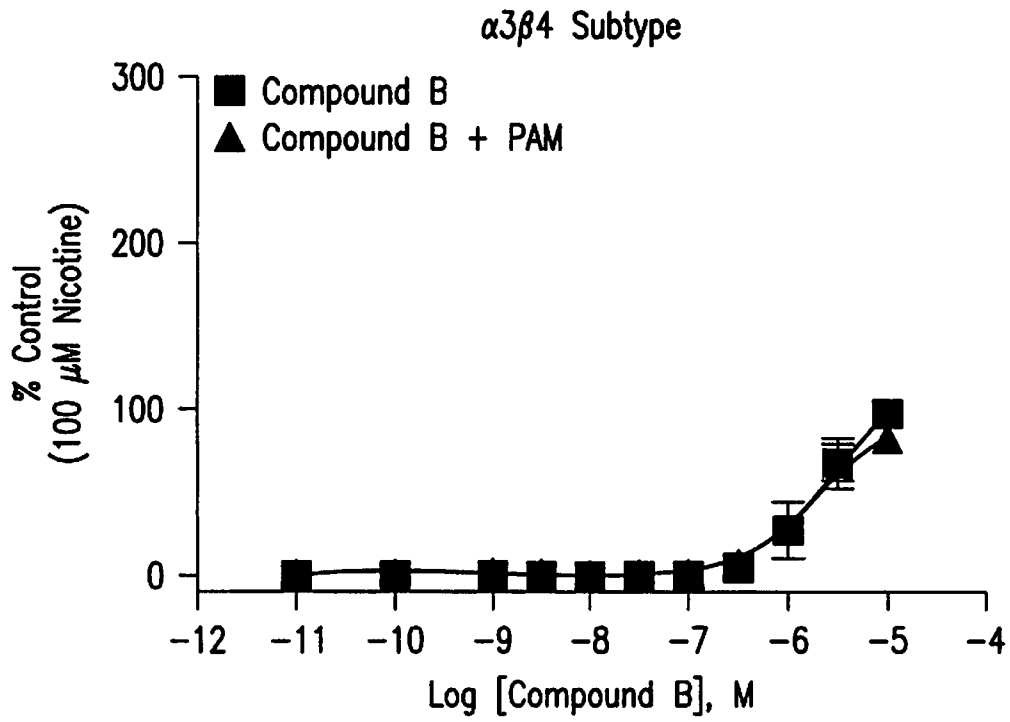


FIG.2B

5/20

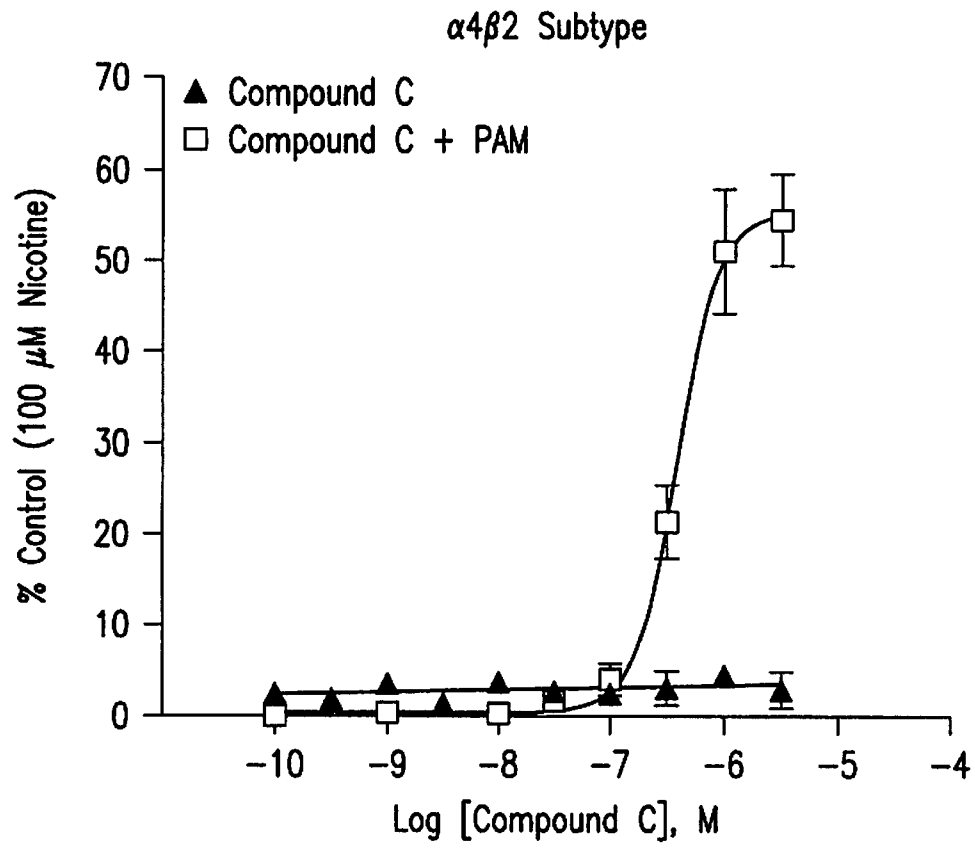


FIG.3A

6/20

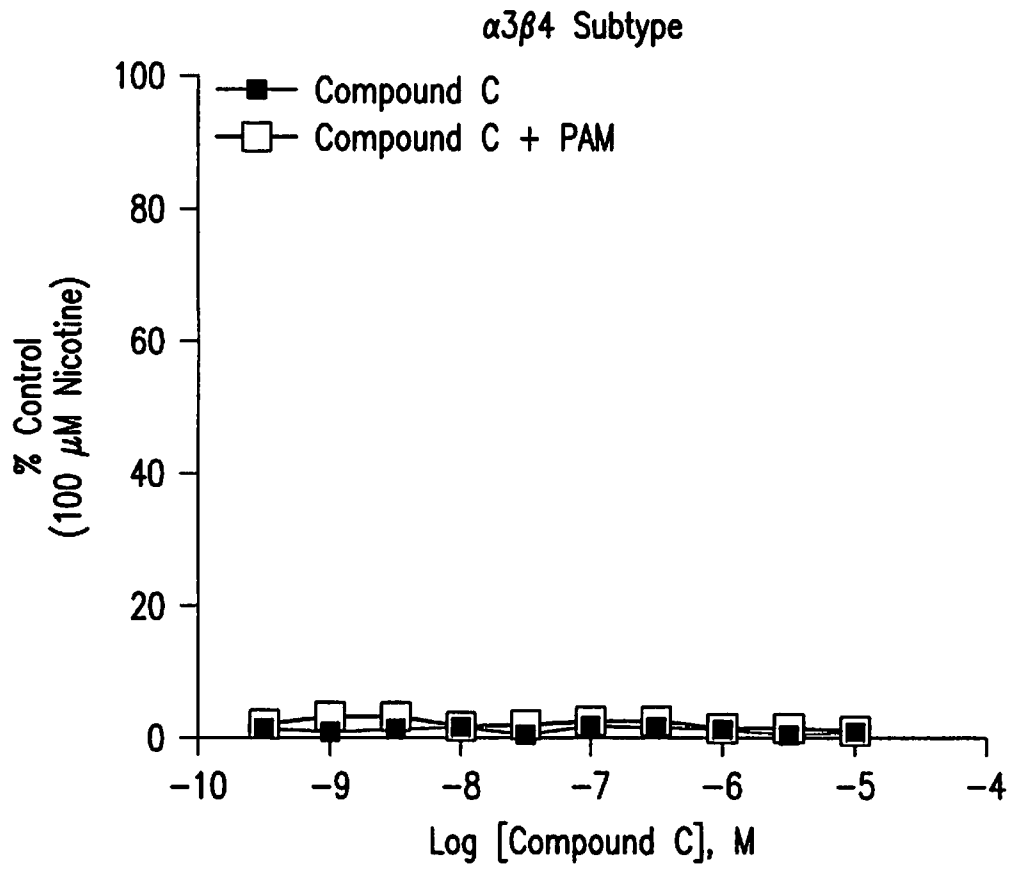
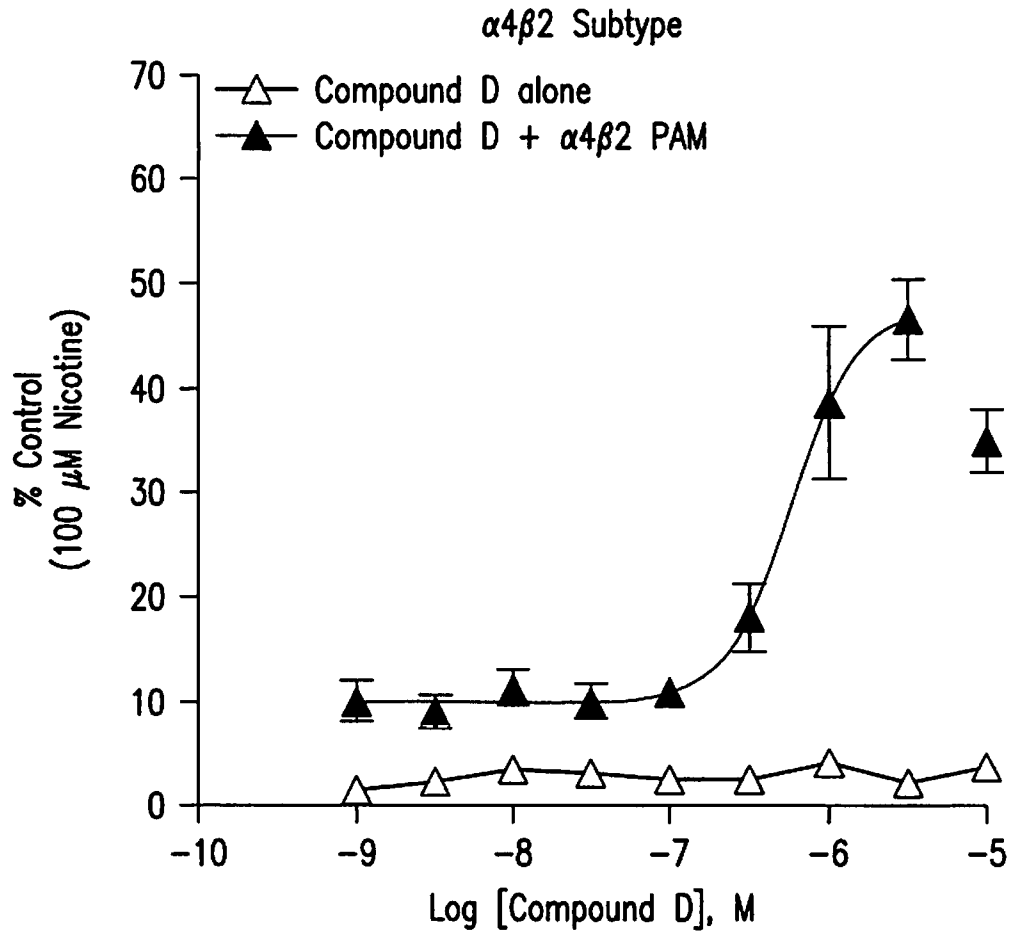


FIG.3B

7/20



**FIG.4A**

8/20

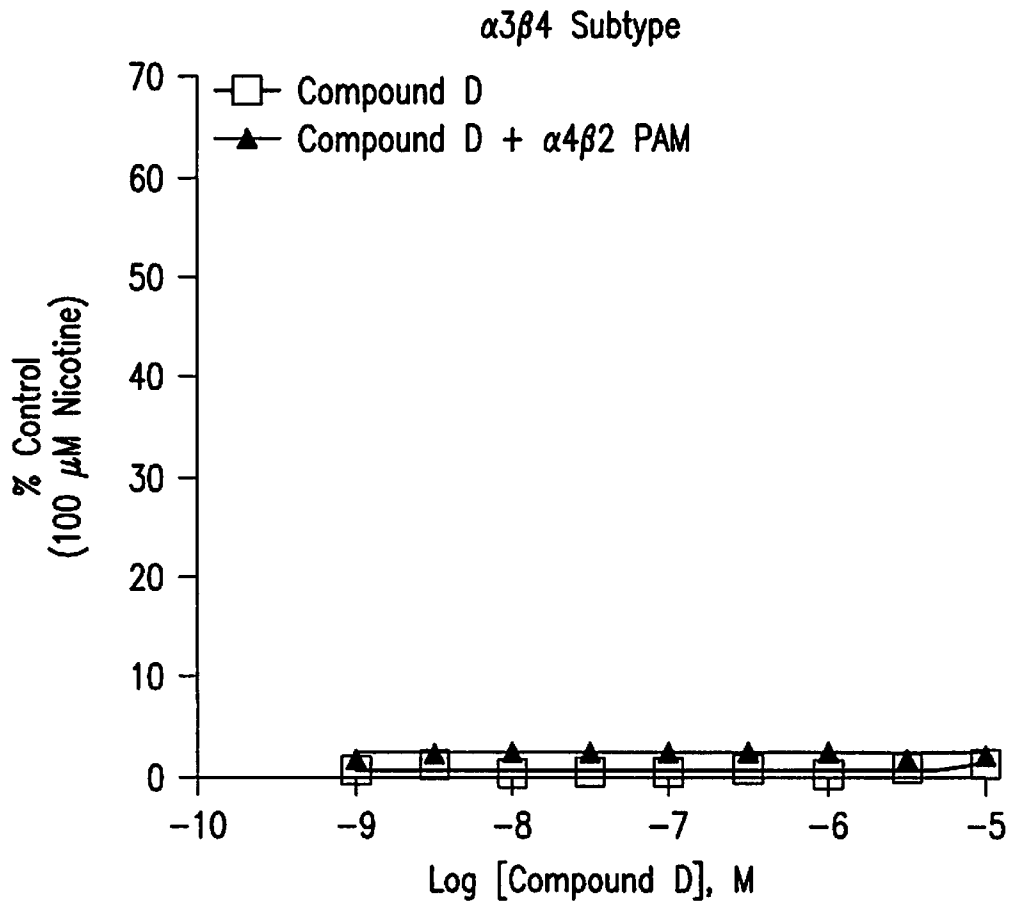


FIG.4B

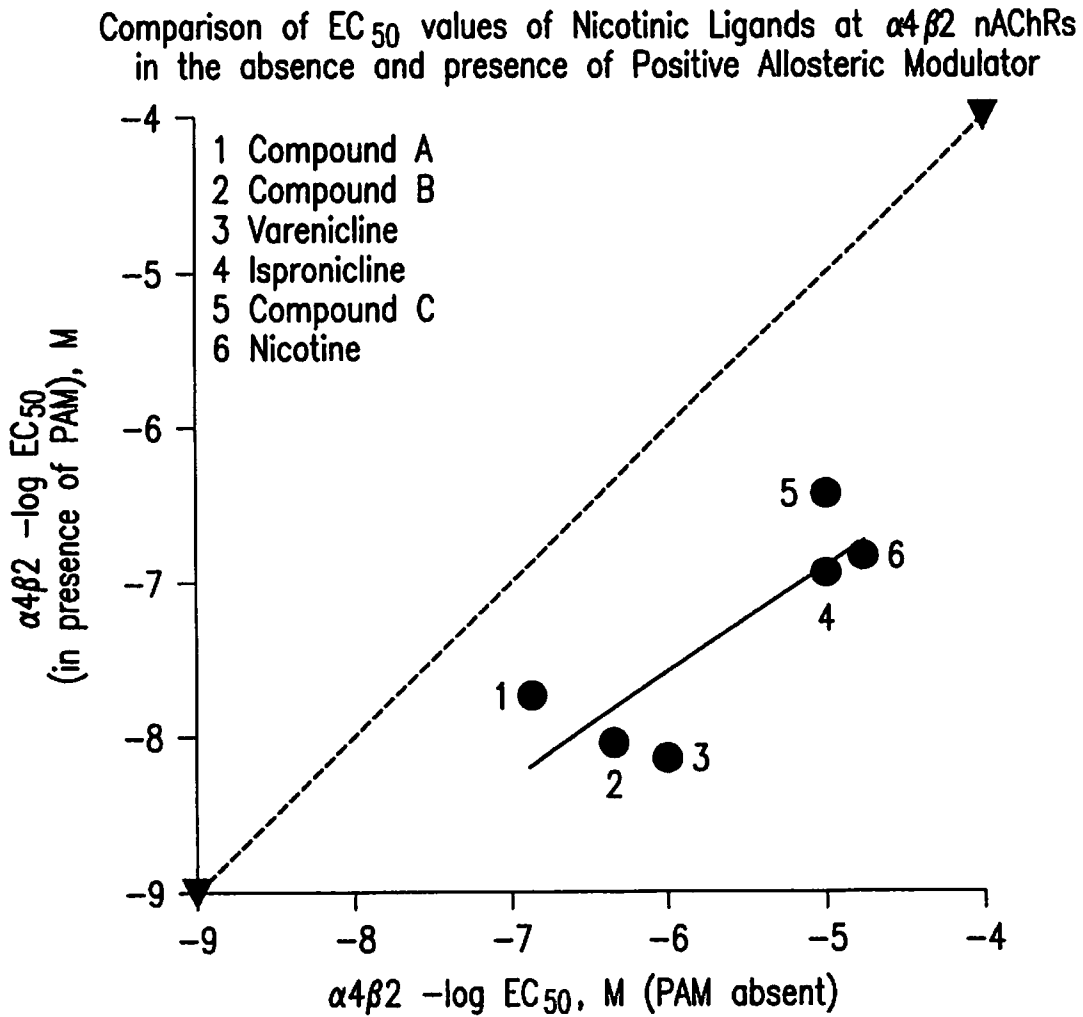


FIG. 5

10/20

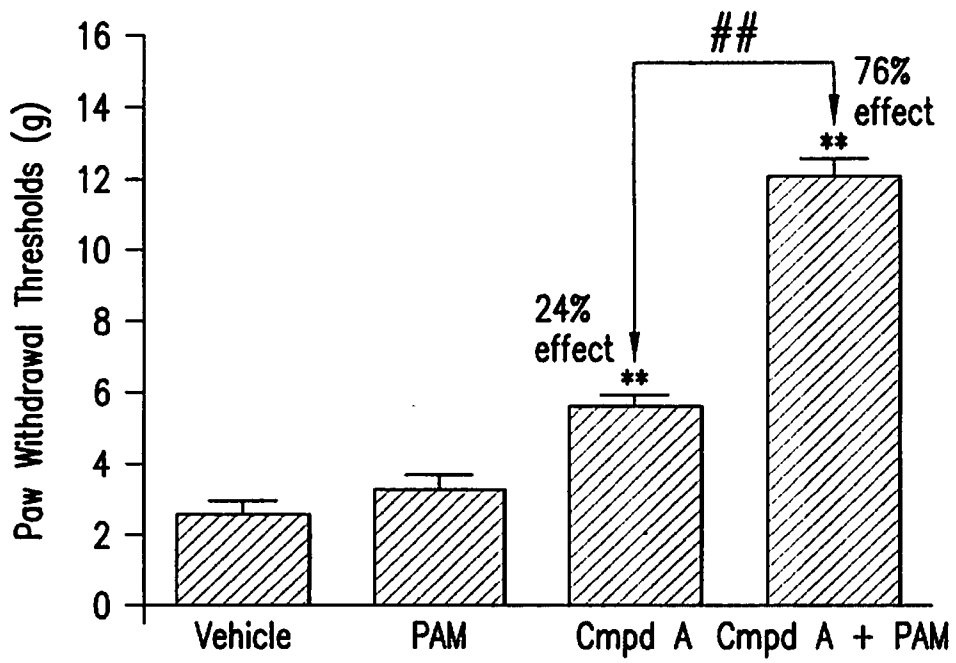


FIG.6A

11/20

Effects of  $\alpha 4\beta 2$  PAM are Dose Dependent: An ineffective dose of Compound A (1nmol/kg) is as Efficacious as Gabapentin in presence of  $\alpha 4\beta 2$  PAM

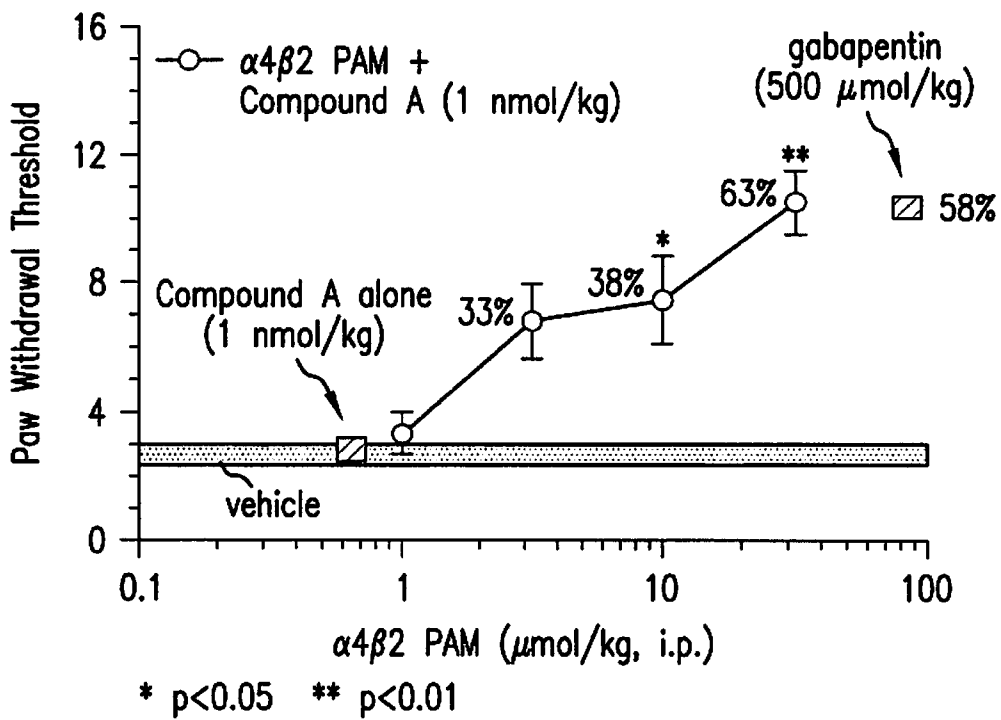


FIG.6B

12/20

Combination of  $\alpha 4\beta 2$  PAM Left Shifts the Neuropathic Pain Efficacy Dose Response Curve of Compound A in the Chung Model

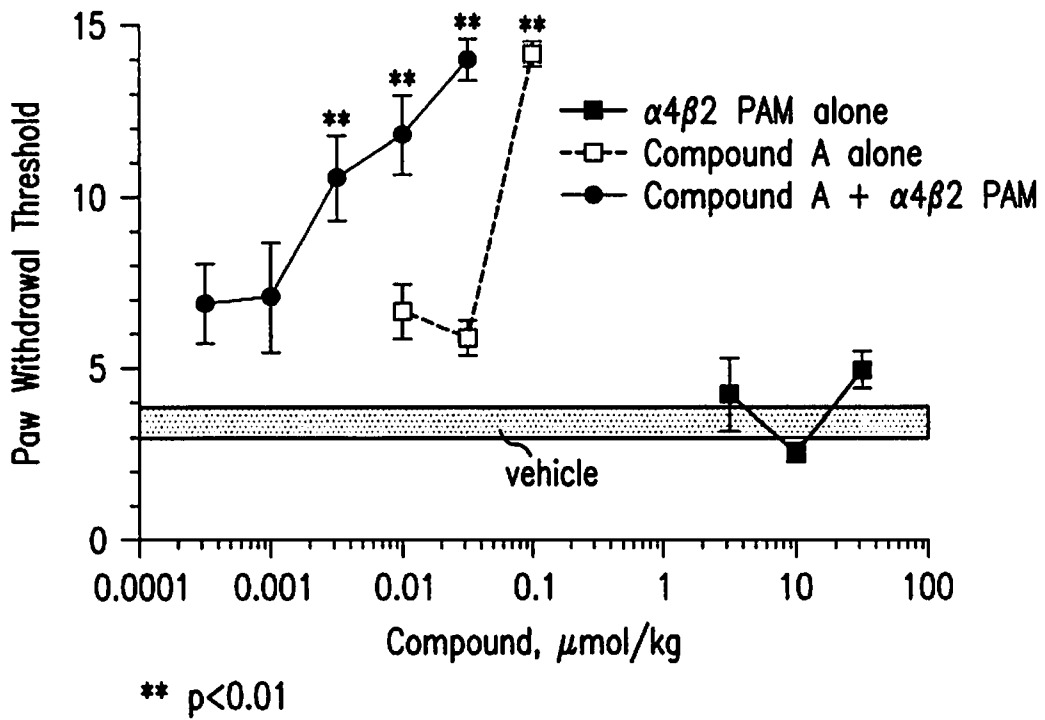


FIG.7A

Combination of  $\alpha 4\beta 2$  PAM with Compound A Does Not Shift Emesis Dose Response Curve in Ferrets

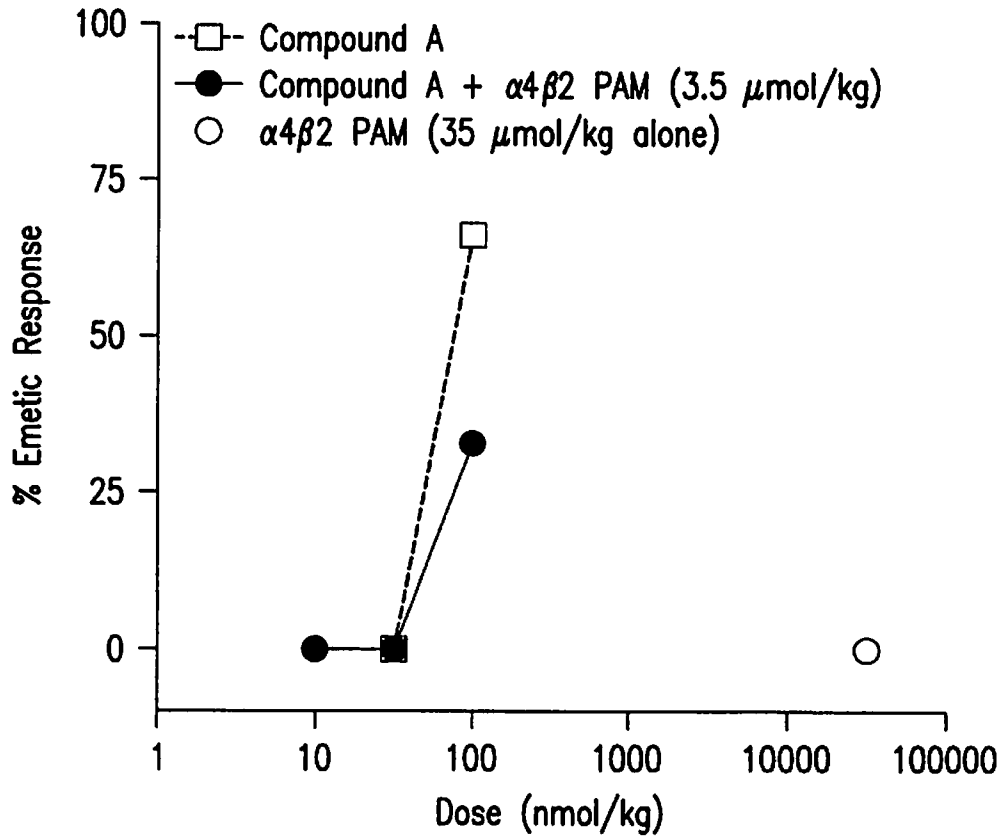


FIG.7B

14/20

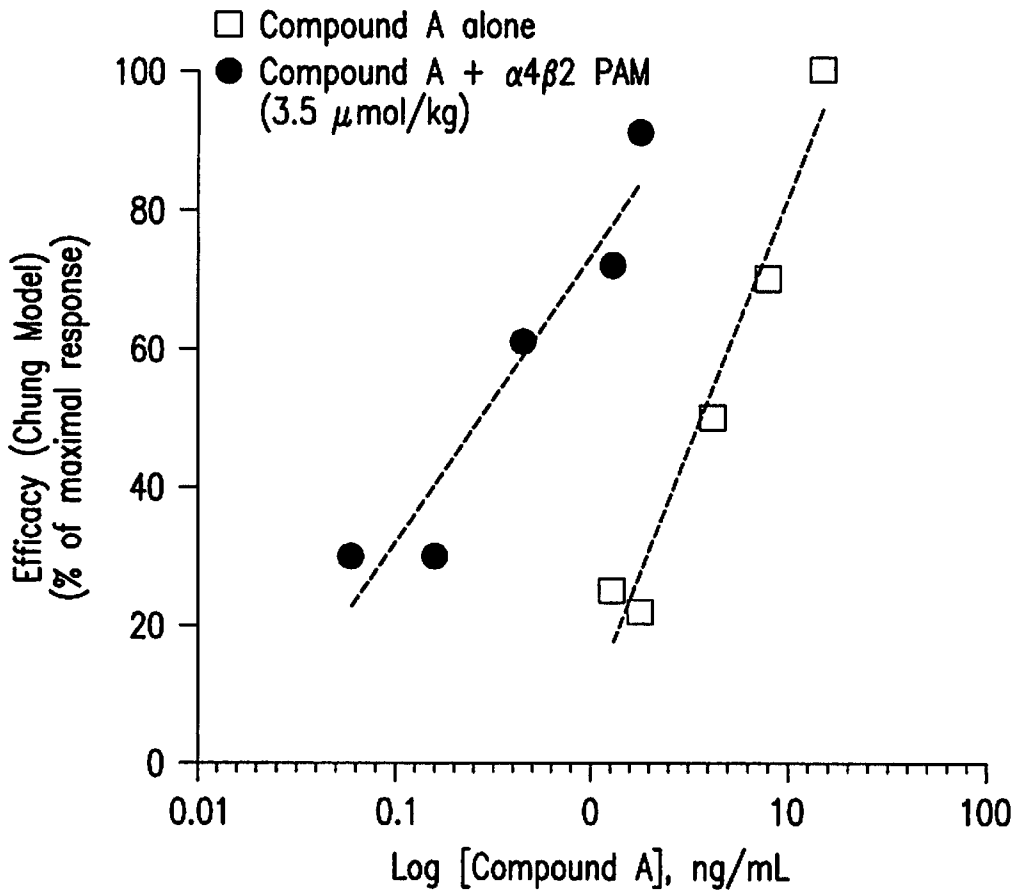


FIG.8A

15/20

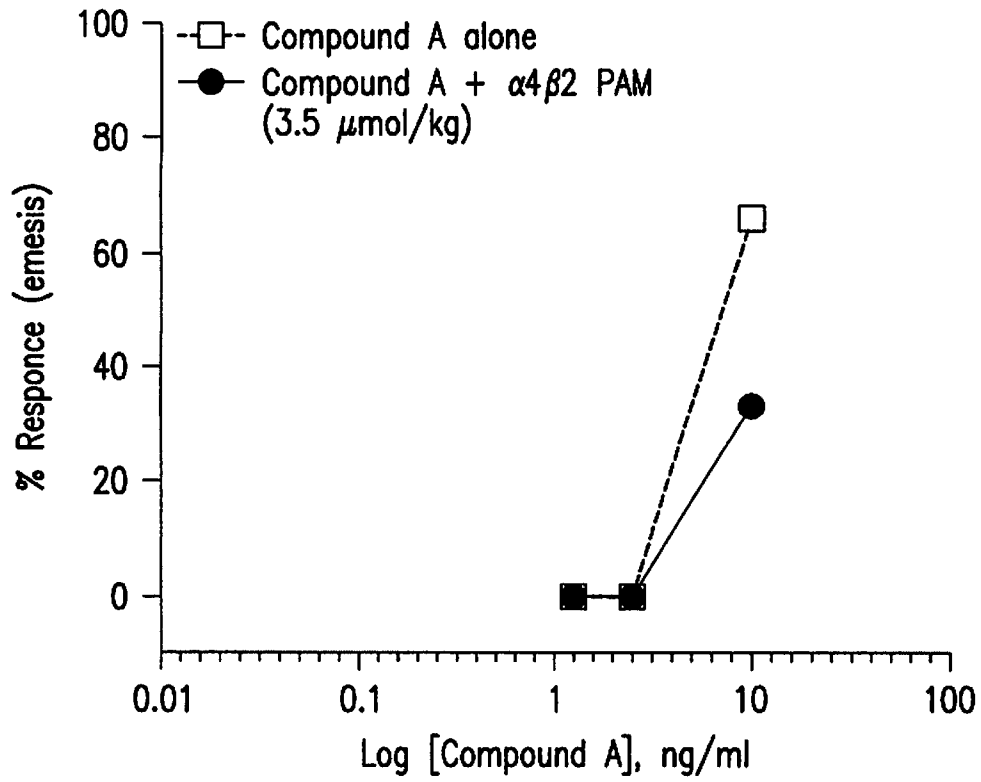


FIG.8B

16/20

Compound D (nAChR partial agonist) is ineffective alone in neuropathic pain, but when combined with  $\alpha 4\beta 2$  PAM, is effective

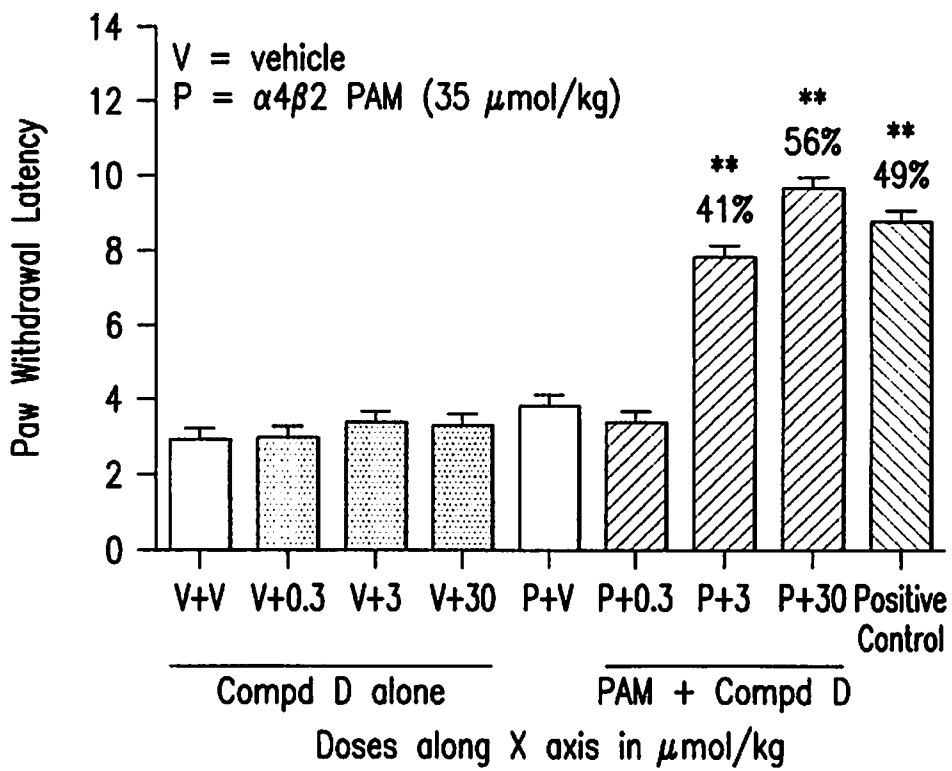


FIG.9

17/20

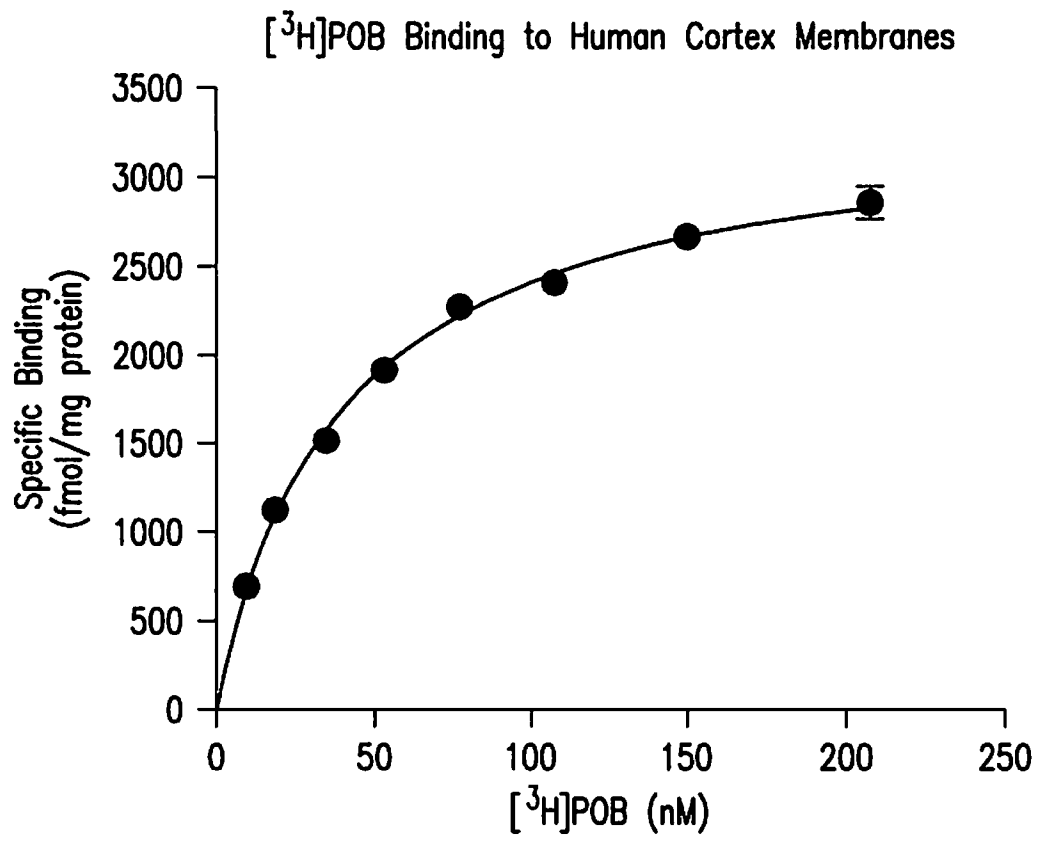


FIG. 10

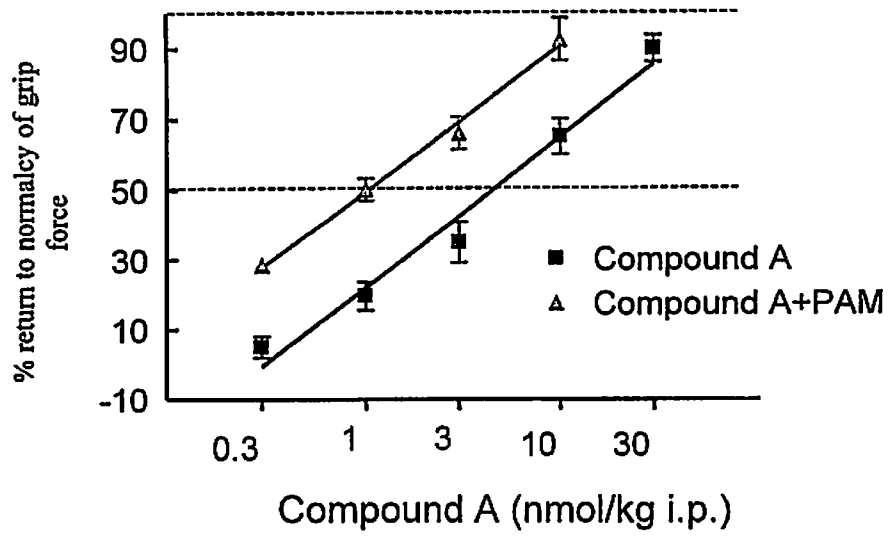


FIG. 11

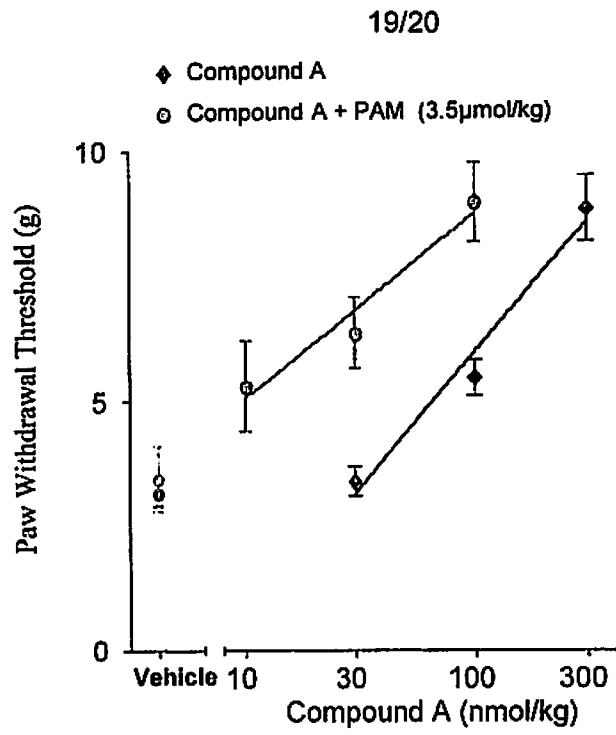


FIG. 12

20/20

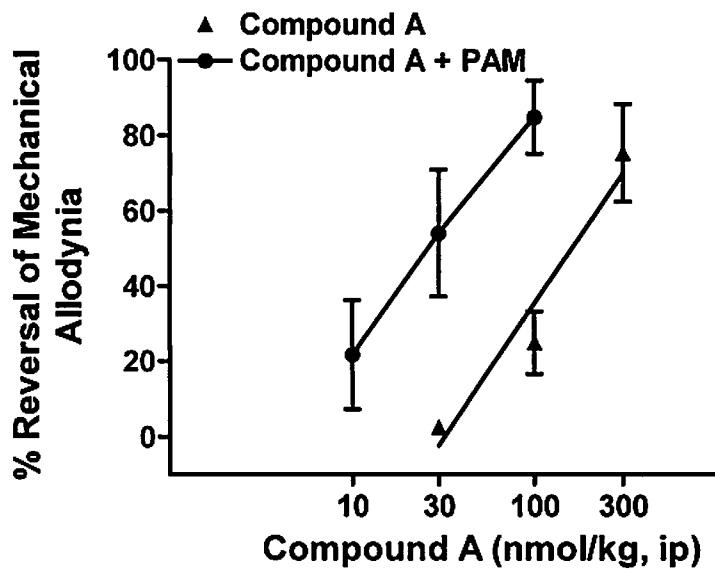


FIG. 13